The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

TREATMENT OF OBESITY: DEVELOPMENTS OF THE PAST 150 YEARS—*A. W. Pennington, M. D.* 65

PATHOPHYSIOLOGY OF OBESITY—*A. W. Pennington, M. D.* 69

THE SOLUBILITY OF SOME SULFONAMIDES OF CURRENT CLINICAL IMPORTANCE—*J. B. Ziegler, R. E. Bagdon and A. C. Shabica* 74

PRIMARY JEJUNAL ULCER: AN UNUSUAL CAUSE FOR SEVERE ANEMIA—*Michael Muehlbauer, M. D., Albert Kramer, M. D. and Bernard Epstein, M. D.* 77

CLINICAL COMPARISON OF FOUR ANTICHOLINERGIC DRUGS—*Jacob A. Riese, M. D.* 81

PSEUDO-HOOKWORM—*Lt. H. M. Spiro, M. C., Capt. C. N. Shropshire, M. C. and Col. E. S. Fugelso, M. C.* 83

ABSTRACTS ON NUTRITION, EDITORIALS, BOOK REVIEWS, GENERAL ABSTRACTS OF CURRENT LITERATURE 86-92

Volume 21 March, 1954 Number 3

Copyright 1954, Sandfield Publishing Company

The antacid
as pleasant
as an
after-dinner mint

ALUDROX®

Aluminum Hydroxide Gel with
Magnesium Hydroxide

For rapid relief of
simple hyperacidity
or the hyperacidity
of peptic ulcer

When an antacid is prescribed, the physician wants medical effectiveness. When the antacid is taken, the patient wants palatability and convenience.

ALUDROX Tablets combine these qualities. They afford efficient antacid therapy. They are unobtrusive, pleasant to take . . . can be chewed and swallowed with or without water, wherever the patient may be. Tablets encased in handy cellophane strips, to fit pocket or purse.

Supplied:
ALUDROX Tablets,
boxes of 60

Also available:
ALUDROX Suspension,
bottles of 12 fl. oz.

ALUDROX

Wyeth®
PHILADELPHIA 2, PA.

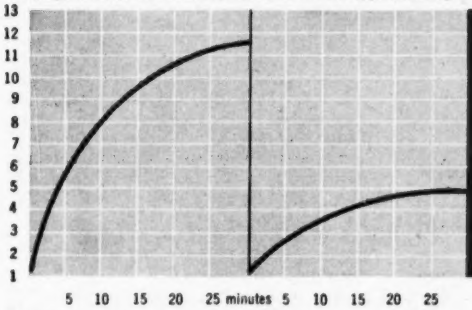
"It's a great relief..."

and 8000 doctors agree*

For acid indigestion, heartburn, bloating, belching and dyspepsia, 8000 doctors say they rely on Creamalin, *the reactive gel,* to give relief.

Because it is reactive,
Creamalin excels nonreactive gels
... in acid-combining power
... in buffering capacity (Creamalin combines with at least 12 times its volume N/10 HCl in less than thirty minutes[1])
... in speed and completeness of reaction[2]

Superiority of *reactive* Creamalin in hyperacidity



"The reactive form reacts completely in a relatively short time."[2]

"The nonreactive form remains in ... suspension ... for prolonged periods."[2]

Creamalin
reactive gel
LIQUID AND TABLETS

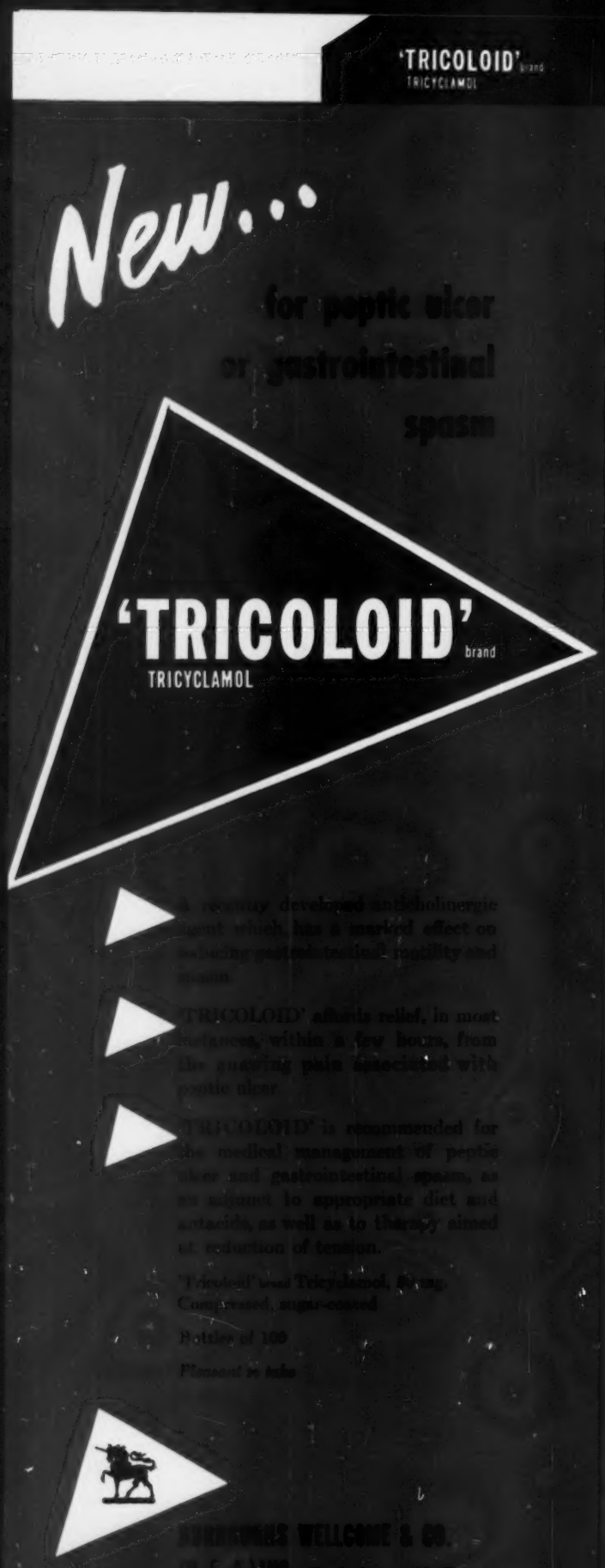
WINTHROP

Creamalin—in pregnancy heartburn
Creamalin tablets act without acid rebound or electrolyte imbalance, cause no fluid retention. They add virtually no calories. Palatable and of smooth consistency, Creamalin tablets are easy to take. Prescribe as often as necessary.

1. *Woldman, E. E.:* Am. Jour. Med. Sc., *194:333, Sept., 1937.*
2. *Smith, F. H.:* Gastroenterology, *8:494, Apr., 1947.*

Winthrop-Stearns INC. New York 18, N. Y. Windsor, Ont.

*Answers to a questionnaire recently mailed to 65,000 physicians
Creamalin, trademark reg. U. S. & Canada, brand of aluminum hydroxide gel



THE OLDEST PERIODICAL IN ITS SPECIAL FIELD ON THE WESTERN HEMISPHERE

Printing Office:
117 E. Main St., Berne, Indiana
Business and Editorial Office:
229 West Berry Street, Suite 302-310
Fort Wayne, Indiana
Advertising Office:
Vining & Meyers
35 East Wacker Drive
Chicago 1, Illinois

Annual Subscription Rate, $6.00
Two Years, $10.00
Single Copies: Current Year 80c.
Back Years $1.00
Foreign Subscriptions $7.00; two years $12.00

Editor: Beaumont S. Cornell,
Fort Wayne, Indiana
Associate Editor: Franz J. Lust,
17 E. 89th St., New York, N. Y.

EDITORIAL COUNCIL

Clinical Medicine—Diseases of Digestion: Anthony Bassler; John M. Blackford; Leon Bloch; Arthur Leonard Bloomfield; Russel S. Boles; Edward S. Emery, Jr.; George B. Eusterman; Harry Gauss; Frank D. Gorham; Russell L. Haden; R. H. M. Hardisty; Charles Lester Hartsock; Blair Holcomb; Harry G. Jacobi; Allen A. Jones; Chester M. Jones; Clement Russell Jones; Noble Wiley Jones; Joseph William Larimore; B. B. Vincent Lyon; Lay Martin; Francis D. Murphy; Moses Paulson; George M. Piersol; Milton M. Portis; Martin Rehfuss; Vernon C. Rowland; Adolph Sachs; Leon Schiff; Daniel M. Silverman; Virgil E. Simpson; Albert M. Snell; Cyrus Cressey Sturgis; Martin G. Vorhaus. Gastroscopy, Esophagoscopy: James L. Borland; E. B. Freeman; Chevalier Jackson; Rudolf Schindler; Porter Paisley Vinson. Nutrition: Lloyd Arnold; Clifford Joseph Barborka; Reginald Fitz; Seale Harris; Henry L. John; Howard Frank Root; Nina Simmonds. Surgery of the Lower Colon and Rectum: Louis Arthur Buie; Jerome Morley Lynch; Clement L. Martin; Curtis Rosser; Louis J. Hirschman; Frank C. Yeomans. Bacteriology: Oscar Felsenfeld. Therapeutics: Walter A. Bastedo; Edward S. McCabe. Allergy: Albert H. Rowe; J. Warrick Thomas. Roentgenology: David S. Beilin; Arthur C. Christie; Frederick J. Hodges; William H. Stewart. Parasitology: Robert Hegner; Kenneth Merrill Lynch; Thomas Byrd Magath; Henry Meleney. Experimental Physiology: J. P. Quigley; A. J. Carlson; M. H. F. Friedman; Ira A. Manville; Edward J. Van Liere. Psychiatry and Neurology: William C. Menninger. Abdominal Surgery: Julian A. Sterling; Thomas M. Joyce; Rudolph Matas; Edward Wm. Alton Ochsner; James Taft Pilcher; Charles T. Sturgeon.

Published Monthly at 117 East Main St., Berne, Ind.

Correspondence regarding advertising must be addressed to Vining and Meyers, 35 E. Wacker Drive, Chicago. Advertising plates must be sent to M. I. Lehman, 117 E. East Main St., Berne, Indiana. Subscriptions, reprint orders, etc., should be addressed to 229 West Berry Street, Suite 302-310, Fort Wayne, Indiana. Manuscripts and books for review must be addressed to Dr. Beaumont S. Cornell, 229 West Berry St., Fort Wayne 2, Ind. Illustrations in excess of six per article are charged at cost to the author. Contents of Journal are fully copyrighted. Copyright 1950, by Sandfield Publishing Co., 229 W. Berry St., Fort Wayne, Ind., in the U. S. A. Vol. 21, No. 3, March, 1954. Entered as second class matter, Sept. 6, 1950, at the Post Office at Berne, Indiana, under the Act of March 3, 1879.

Meat...

and Adequate Protein Nutrition of the Diabetic Patient

Although formerly it was considered desirable in diabetes mellitus to hold protein intake only slightly above minimal requirements in order to minimize metabolic activity, present day treatment recognizes distinct benefits resulting from liberal protein alimentation.[1] Generous allowances of protein heighten the patient's sense of well-being, improve vigor, and augment the organism's inherent protective forces.

For the adult diabetic, desirable daily allowances of protein range from 1 to 1.5 grams per kilogram of body weight.[1] To assure adequate amounts of protein for growth and maintenance in diabetic children, allowances should range from 2 to 3 grams per kilogram. Following acute episodes during periods of inadequate insulin treatment, the concomitant negative nitrogen balance calls for high protein feeding until lost nitrogen is restored.[2] Though caloric intake is restricted for correction of overweight, protein allowances remain unchanged.

Meat ranks high among the foods qualified to provide the desired amounts of protein in diabetic diets. In fact, meat—because its rich store of protein is of highest biologic value—may well contribute a large share of the diabetic's daily protein requirement.[3]

In addition, meat also provides important amounts of essential B vitamins and minerals. Its appetite appeal goes far in enabling the diabetic patient to stay on his prescribed diet.

---

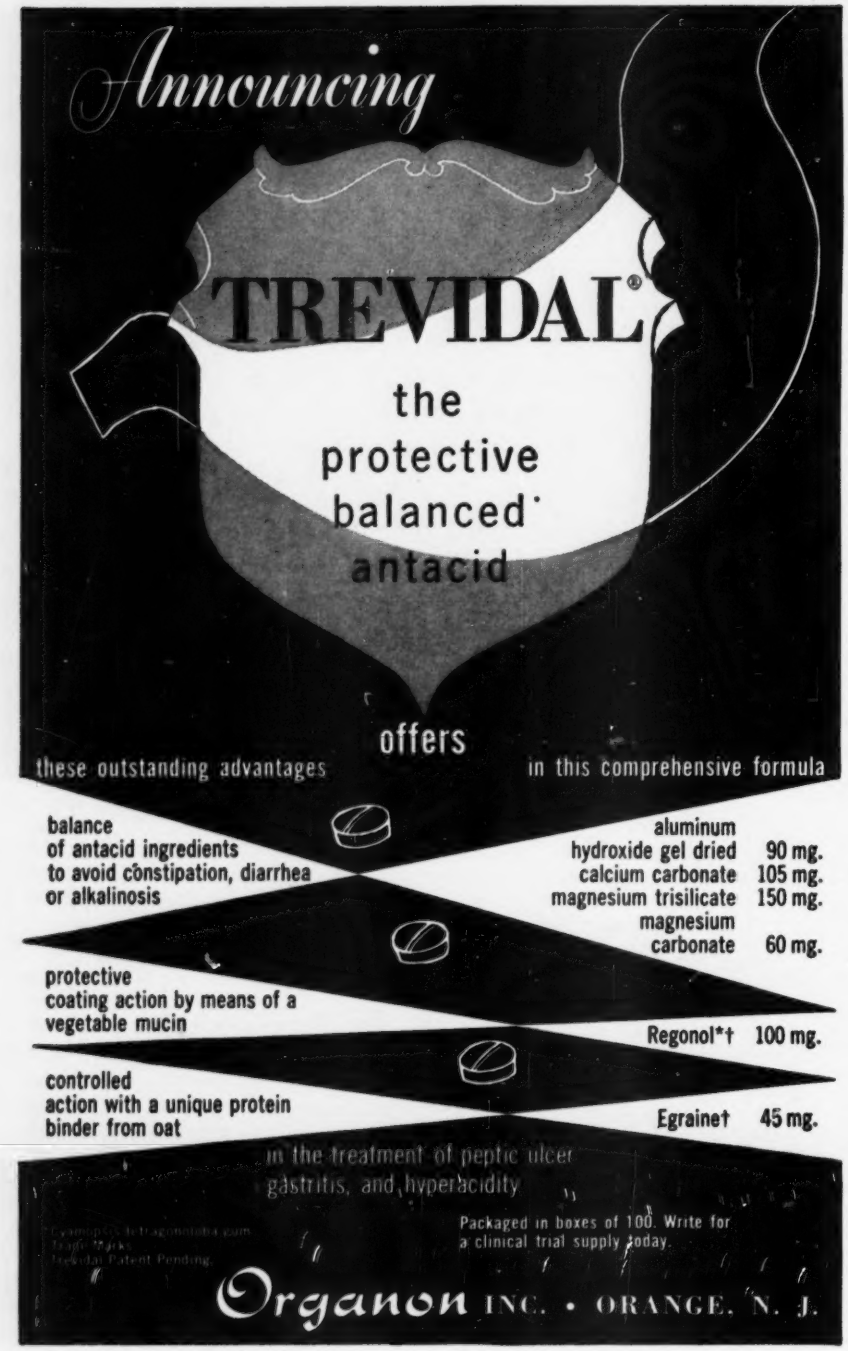
1. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 287-299.

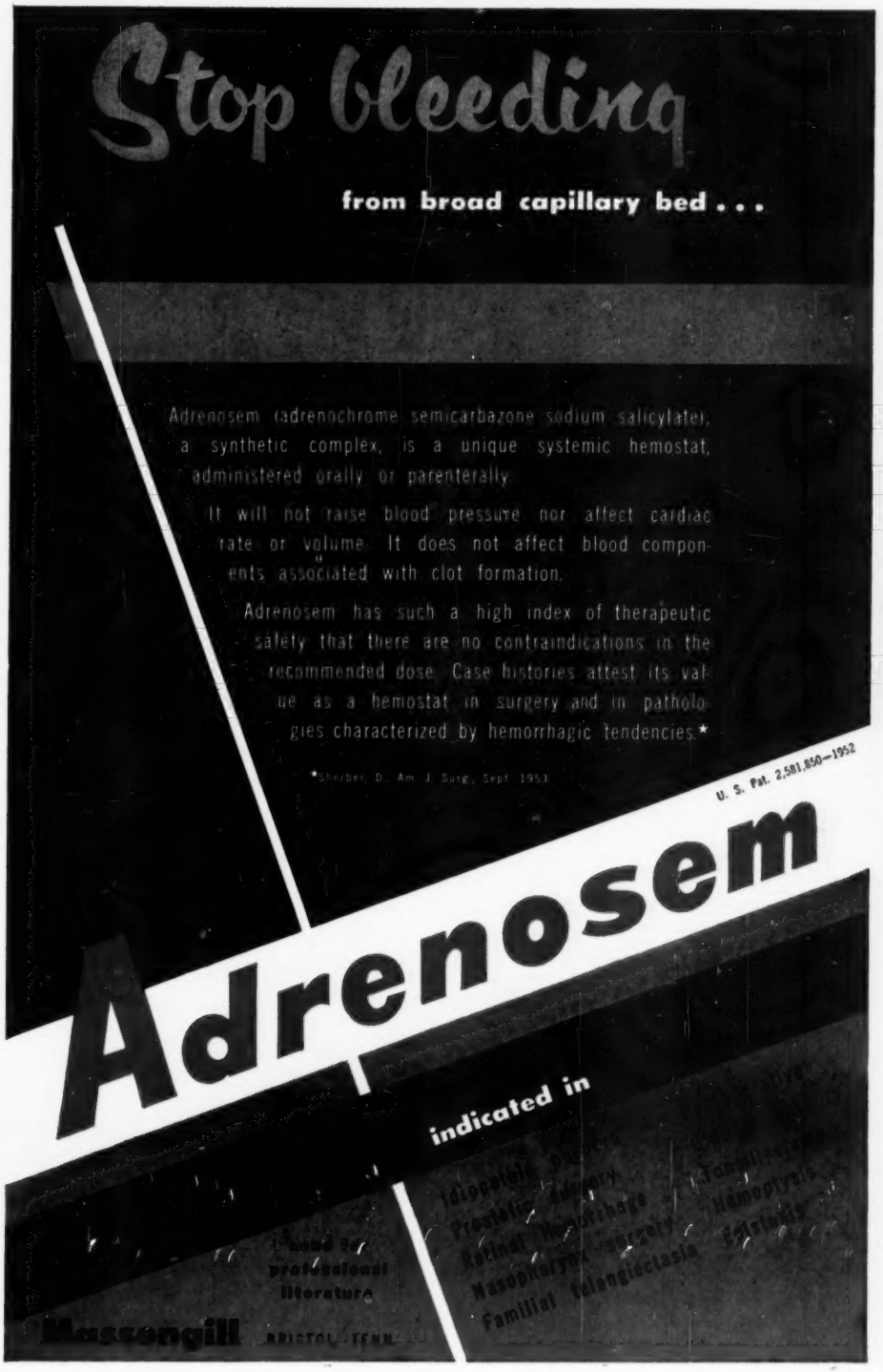
2. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition. Prepared with Collaboration of the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Publication 234, 1952, p. 56.

3. Cecil, R. L., and Loeb, R. F.: A Textbook of Medicine, ed. 8, Philadelphia, W. B. Saunders Company, 1951, p. 634.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

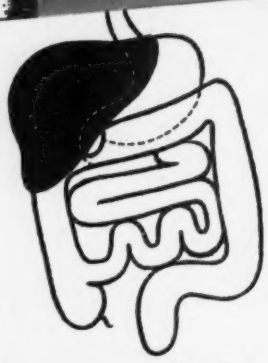
American Meat Institute
Main Office, Chicago...Members Throughout the United States


Announcing
TREVIDAL®
the protective balanced antacid
offers
these outstanding advantages
in this comprehensive formula
balance of antacid ingredients to avoid constipation, diarrhea or alkalinosis
aluminum hydroxide gel dried 90 mg.
calcium carbonate 105 mg.
magnesium trisilicate 150 mg.
magnesium carbonate 60 mg.
protective coating action by means of a vegetable mucin
Regonol*† 100 mg.
controlled action with a unique protein binder from oat
Egrainet 45 mg.
in the treatment of peptic ulcer gastritis, and hyperacidity
Packaged in boxes of 100. Write for a clinical trial supply today.
Trademarks
Trevidal Patent Pending
Organon INC. • ORANGE, N. J.


Stop bleeding
from broad capillary bed . . .
Adrenosem (adrenochrome semicarbazone sodium salicylate), a synthetic complex, is a unique systemic hemostat, administered orally or parenterally.
It will not raise blood pressure nor affect cardiac rate or volume. It does not affect blood components associated with clot formation.
Adrenosem has such a high index of therapeutic safety that there are no contraindications in the recommended dose. Case histories attest its value as a hemostat in surgery and in pathologies characterized by hemorrhagic tendencies.*
*Shreiber, D., Am. J. Surg., Sept. 1953
U. S. Pat. 2,581,850—1952
Adrenosem
indicated in
Idiopathic
Prostatic surgery
Retinal hemorrhage
Nasopharynx surgery
Familial telangiectasia
Hemoptysis
Epistaxis
Sound professional literature
Massengill
BRISTOL, TENN.

it takes more than spasmolysis to relieve functional G. I. distress

Decholin/Belladonna



prescribe these **double benefits**

reliable spasmolysis
inhibits smooth-muscle spasm...
suppresses incoordinate peristalsis...
facilitates biliary and pancreatic drainage

improved liver function
increases bile flow and fluidity through *hydro*choleresis...
enhances blood supply to liver...
provides mild, natural laxation—without catharsis

DECHOLIN® with Belladonna

for prompt, more effective relief of belching, bloating, flatulence, nausea, indigestion and constipation

Dosage: One or, if necessary, two *Decholin*/Belladonna Tablets three times daily.

Composition: Each tablet of *Decholin*/Belladonna contains *Decholin* (dehydrocholic acid, *Ames*) 3¾ gr., and ext. of belladonna, ⅙ gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100.

AMES COMPANY, INC.

ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

54154

large gastric ulcer

Fig. 3, Case 103 before therapy.

healed with

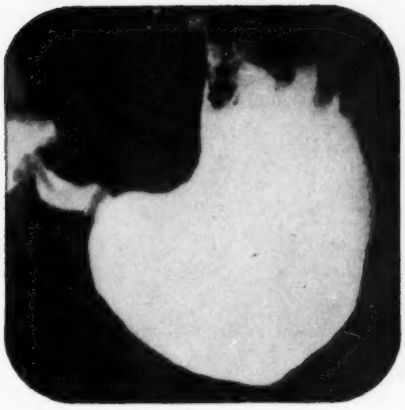


Fig. 6, Case 103 after 4 months PRANTAL therapy.
* Heineken, T. S.: Rev. Gastroenterol. 20:829, 1953.

PRANTAL...*relieves pain*

*facilitates healing • "least side actions"**

widest variety of dosage forms

PRANTAL® Methylsulfate, brand of diphenmethanil methylsulfate.

Schering

PRANTAL

Ciba products of performance

Antrenyl®

BROMIDE

(OXYPHENONIUM BROMIDE CIBA)

for demonstrable benefit in peptic ulcer

THE PATIENT FEELS

ulcer pain is rapidly controlled (often within 24-36 hours); relief lasts with continuing treatment.

YOU OBSERVE

almost uniformly good response and progress toward healing; few and generally mild by-effects.

THE LITERATURE REPORTS

50 out of 52 responding to Antrenyl; [1] complete relief in *all* of 24 cases; [2] 33 of 39 patients healed or improved. [3] Antrenyl is a valuable adjunct to dietary and other ulcer measures. Tablets, 5 mg., Syrup, 5 mg. per 4 ml.

1. Rowen, B.R., Bachrach, W.H., Halsted, J.A., and Schapiro, H.: Gastroenterology 24:86, 1953.

2. Rogers, M.P., and Gray, C.L.: Am. J. Digest. Dis. 19:180, 1952.

3. Schaub, K.: Praxis 41:1073, 1952.

Ciba *Summit, N. J.*

TREATMENT OF OBESITY: DEVELOPMENTS OF THE PAST 150 YEARS

A. W. Pennington, M. D., Wilmington, Del.

THE CONCEPT that common obesity arises from some cause other than simple overfeeding has, in the past, suffered from lack of an effective treatment to fit a proposed rationale and also, in at least one instance, from lack of a rationale to fit an effective treatment.

Thomas Beddoes and William Wadd

An example of the first of these disadvantages occurred at the end of the 18th century. Dr. Thomas Beddoes (1), in 1793, applied the new "theory of pneumatic chemistry" that had arisen from the experiments of M. Lavoisier in France. This theory held that the respiratory tract of the living body took in oxygen, combined it with carbon derived from foodstuffs, and expelled the carbon in combination with the oxygen. Dr. Beddoes cited evidence that oxygen, when taken into the body, went deeper than the lungs, and he suspected that obesity might be caused by an insufficient admixture of oxygen with body fat. Applying this early theory of obesity as a defect of the intermediary metabolism, he attempted to remedy the condition by introducing more oxygen into the system. His theory, however, was easily disposed of by William Wadd, who observed, "Dr. Beddoes remained so inconveniently fat during his life that a lady of Clifton used to denominate him the walking feather bed" (2).

William Wadd, Surgeon-Extraordinary to the Prince Regent, was a champion of orthodoxy in medical thought. He maintained a reserved attitude toward the idea of oxygen diffusing widely through the body, and toward the intricacies of its alleged combination with fat. He attributed obesity to "an overindulgence of the table," the overindulgence, in turn, being explained by phrenology as a disturbance of the "organ of gustativeness" (3). Wadd cited as the first principle of treatment, "taking food that has little nutrition in it." His views prevailed, for he could show that their application resulted in weight reduction.

William Harvey and His Patient, Mr. Banting

An example of the second disadvantage, that of an effective treatment without a rationale, occurred at the middle of the 19th century; and to appreciate the significance of this remarkable story, it is helpful to understand the prevailing views at that time. The writings of William Wadd had come to hold classic rank on the subject of obesity; but more details of physiology had been brought to light, and Wadd's views were now being restated in terms of the physiology of Liebig. According to Liebig, carbohydrate and fat supplied the carbon that was believed to combine with oxygen in the lungs for the purpose of producing body heat; carbohydrate and fat, accordingly, were called "respiratory foods" (4). The pathogenesis of obesity was summed up in 1850 as follows: "For the formation of body fat it is necessary that the materials be digested in a greater quantity than is necessary to supply carbon to the respiration" (5). The chief principle of treatment was to cut off, as far as possible, the supply of materials, especially dietary fat; and to accomplish this it was necessary for the patient to establish an "hourly watch over the instinctive desires."

Submitted Sept. 17, 1953.
Med. Div. E. I. du Pont deNemours & Co.

With this background of medical indoctrination an English ear surgeon, named William Harvey (6), went to Paris in 1856 and attended the lectures of Claude Bernard. He was greatly impressed with Bernard's new theory that the liver secreted not only bile but also a peculiar substance, allied to starches and sugars, to which the name glucose had been given. Reflecting upon such matters as the then well-known fact that "a purely animal diet greatly assisted in checking the secretion of diabetic urine," and that "a saccharine and farinaceous diet is used to fatten certain farm animals," it occurred to him "that excessive obesity might be allied to diabetes as to its cause, although widely diverse in its development; and that if a purely animal diet were useful in the latter disease, a combination of animal food with such vegetable diet as contained neither sugar nor starch, might serve to arrest the undue formation of fat."

This theory of obesity as a disturbance in the intermediary metabolism of carbohydrate left many questions unanswered; for, as Harvey observed, "the lights of chemistry, feeble as they are in the stomach and first intestine, fail us altogether after the change produced by the admixture of bile." It was, however, a simple matter for him to test out his theory. An extremely corpulent gentleman, in his 60's, consulted him for deafness. Finding no organic disease of the ear, Harvey suspected the trouble arose from the pressure of fat on the Eustacian tubes, and he prescribed "a strict non-farinaceous and non-saccharine diet." Meats, including venison, poultry and fish, were allowed in amounts upward of 24 ounces a day. No mention was made of trimming off the fat. Some foods containing sugar and starch were allowed in limited quantities, partly, it seems, because the exact composition of them was not known at the time. Certain alcoholic beverages, also, were allowed, in the belief that alcohol, like water, was completely excreted by the body.

The patient, whose name was William Banting, did well on the diet. Although his weight was not reduced completely to normal, he lost 46 pounds in the course of a year while eating of the diet to the free satisfaction of his appetite (7). His hearing was restored, his general health was improved, and the many inconveniences of his extreme obesity were greatly lessened. Gratified at the relief obtained through so pleasant and easy a treatment, he wrote and had published a pamphlet that first made its appearance in 1863. The pamphlet was circulated widely and the treatment was phenomenally successful. The "Banting diet," then, became the center of a stormy controversy.

No one could doubt that the unorthodox treatment was effective. Having made its appearance in a lay publication, however, it was given a chilly greeting

by the medical profession, and it was criticized as being unscientific, freakish and too expensive. In addition, it was said to be "old as the hills." Harvey, in his practice as an ear surgeon, was subjected to much ridicule and vituperation as a result of his successful experiment with a "non-farinaceous and non-saccharine diet." The practical success of the diet, however, compelled "the faculty" to give an explanation for its effectiveness. This was furnished by Dr. Niemeyer at Stuttgart. Dr. Niemeyer applied the prevailing physiology of Liebig, explaining that protein foods are not converted to body fat but that the "respiratory foods," carbohydrate and fat, are so converted. He interpreted "meat" as "lean meat" and described the diet in terms which, in the present day, would mean that it was a high protein, low calorie diet, with fat and carbohydrate both restricted (7). Although Banting's published correspondence shows that obese people lost weight effectively though partaking largely of the fat of meat (7), Dr. Niemeyer's explanation found acceptance, and "modified Banting" diets found their way into the standard textbooks during the remainder of the century.

In the process of making the diet orthodox, however, two things had to give way. First, Harvey's original theory of obesity was laid aside and, second, his diet became changed beyond recognition. In both of these, Harvey was somewhat of an accomplice. Nine years after Banting's pamphlet first appeared, Harvey published a book which he hoped would "possibly prevent much misunderstanding" (6). In the intervening years, Dr. Niemeyer's explanation had been circulated and the diet, modified to conform with Liebig's physiology, had received the official stamp of approval. Much of Harvey's book was devoted to a discussion of the anatomy, pathology and treatment of diseases of the ear, nose and throat, leaving no doubt that Harvey was well informed in this field. He approached the subject of diet in a rather apologetic way. "Had Mr. Banting not suffered from deafness," he explained, "the probability is that his pamphlet would not have appeared" (6). Harvey mentioned the early reflections that had led him to prescribe a "non-saccharine and non-farinaceous" diet for Mr. Banting, and recommended that it be modified as circumstances required in others. "In the diet," he said, "I usually forbid or place great restriction on all saccharine and fatty matters;" he explained, echoing Dr. Niemeyer, "they are the chief elements of what is called respiratory food, and thereby load the pulmonary machinery."

Thus, Harvey recanted and was able to pursue a peaceful career as a respectable ear surgeon. Banting, his first patient, however, stuck to the original principle of avoiding saccharine and farinaceous foods as he knew them. Although there appears to have been a considerable lack of knowledge as to the precise constituents of some foodstuffs, Banting emphasized his "firm belief and conviction that the *quality* in food is the chief desideratum and that the question of *quantity* is mere moonshine." He maintained his weight loss without difficulty (7) and lived to age 81 (8).

THE POST-BANTING ERA

In the modified Banting diets that followed, emphasis was placed, as it had been before Banting, on a reduction in the food intake. The high protein principle became established, but dietary fat became so restricted that in Allbutt's System of Medicine (9), "Bantingism" was denounced because its severe limitation of fat caused digestive disturbances. Salisbury (10), Oertel (11) and von Noorden (12) evolved high protein, low fat diets. Ebstein (13), however, reacting against the low fat intake that had become associated with the Banting dietary, restricted carbohydrates and allowed more liberal amounts of fat, remarking, at the same time, that "Banting's own dietary system is less unfavorable to fats than are the prescriptions of subsequent observers." The relative satiety values of fat and carbohydrate were hotly disputed, Ebstein favoring fat and von Noorden, carbohydrate. The diet of Germaine Seé (14) followed the pattern laid down by Ebstein, about half of the calories of this low calorie diet being obtained from fat.

In the succession of diets that followed the publication of Banting's pamphlet, every variation in the proportions of the three major foodstuffs was tried, while restricting the total food intake. The high protein principle prevailed generally until the turn of the century, when it fell into the discard as a result of Chittenden's indictment of protein as the cause of many diseases (15). The treatment of obesity, then, reverted essentially to the simple principle of William Wadd. "Restricting the caloric intake" became the euphemism for "taking food that has little nutrition in it."

It seems, from the history of "Bantingism," that Harvey had introduced something of great value. His diet might have been even more successful than it was if the effects of elimination of alcohol and greater restriction of carbohydrate had been tried in conjunction with an unrestricted diet of protein and fat. Exploration of these matters, as the precise constituents of foodstuffs came to be better known, would have tested, further, his original concept. Current nutritional theory, however, did not allow for the possibility of weight reduction without enforcing a restriction of the total food intake. Consequently, the diet was explained, as far as possible, in terms of current theory, and where explanations ran short, the diet was modified "to overcome the theoretical objections." Thus, omniscience remained inviolate and an opportunity for scientific advance was lost.

TREATMENT OF OBESITY IN THE TWENTIETH CENTURY

In the early part of the 20th century, the history of obesity repeated, very much, that of a hundred years before, except that the principle of balance between intake and outgo received greater attention. Thus von Bergmann (16), as Beddoes had done, over a century previously, suggested a diminished oxidation of fat as a cause of obesity, but fat oxidation was now considered in its relation to the rate of fat formation. The "lipophilia" school of thought, as von Bergmann and his successors came to be called, explored the endocrine system and the intermediary metabolism, and they found a number of indications that the metabolism of the obese was altered from normal. Their idea of the adipose tissues of the obese as having a special affinity for fat was only a small, and not essential, part of the whole lipophilia concept; but since it was the point usually singled out for attack it was

the best known. As with the concept of Thomas Beddoes, the great disadvantage of the highly scientific school of thought originated by von Bergmann was the lack of any effective treatment to fit it, specifically.

As the 20th century advanced, the view became ever more widely accepted that the cause of obesity was an inflow of energy greater than the outflow, the disproportion between the two being attributed to careless or perverted eating habits. These, in turn, were explained on a psychiatric or moral basis to which, later, a disorder of the "appestat" was joined. These views on obesity seemed to find ample confirmation in energy balance studies, which appeared to show that weight-loss could be predicted from the calorie deficit of a diet In 1930 Newburgh and Johnston summed up the matter thus: "In conclusion we wish to commit ourselves to the statement that obesity is never directly caused by abnormal metabolism but that it is always due to food habits not adjusted to the metabolic requirements" (17). After all the work that had been done on obesity, this positive and authoritative statement seemed conclusive.

DR. BLAKE F. DONALDSON

With this background of 20th century indoctrination on obesity, many physicians were amazed, in the year 1944 and thereabouts, to see demonstrated at clinical conferences in the New York City Hospital, cases of obesity that were being treated effectively by diets in which meat was allowed in amounts of 24 ounces and upward a day, and in which, in order that there would be no mistaking the matter, it was urged that ¼ of this amount, by weight, should be fat, and the other ¾ lean. Some of the less concentrated carbohydrate foods were allowed in strictly limited amounts, but patients were encouraged to eat meat, the lean and the fat, to the complete satisfaction of their appetites. This treatment was being used by Dr. Blake F. Donaldson.

It was a simple matter to test this treatment on other patients who could be observed more closely; and it appeared that the demonstrated facts were not mere exceptional occurrences that could be dismissed by some plausible explanation. Here was a treatment that, in its encouragement to eat plentifully, to the full satisfaction of the appetite, seemed to oppose not only the prevailing theory of obesity but, in addition, principles basic to the biological sciences and other sciences as well. It produced a sense of puzzlement that was a mighty stimulant to thought on the matter. First impressions, that the explanation must lie in the satiety value of fat or in a reduced food intake consequent to monotony of diet, were quickly overthrown by finding that skeptical patients, who enjoyed the food very much, put the diet to the most severe test possible by eating very copiously of the foods allowed *ad libitum*. The explanation, whatever it might be, seemed to lie much deeper; and it seemed that it would be of value to science to fathom it. Furthermore, the usual treatment of obesity, by caloric restriction, was not outstandingly successful, even in cardiac patients who knew the importance of reducing their weight.

On all sides, concepts of obesity were being dismissed with laconic references to the law of conservation of energy, accompanied by knowing nods. What did not seem to be generally known, however, was that the law of conservation of energy makes no distinction between cause and effect. A positive caloric balance might be the cause of obesity, or, on the other hand, abnormal metabolic processes of obesity might cause a positive caloric balance; and, likewise, a negative caloric balance could reduce the weight, or, on the other hand, physiological forces of weight reduction might be set in motion to establish a negative caloric balance. Repetitive references to the law of conservation of energy in connection with a question in which it was not an issue at all, obviously amounted to nothing more than pious incantations. These tended to distract the general attention from examination of the evidence on the real question, whether or not common obesity arises from a metabolic defect.

AN INVESTIGATION OF THE NATURE OF OBESITY

To find an answer to the puzzle it soon became clear that new energy balance studies could offer little or nothing. No one could doubt that the caloric expenditure was greater than the intake when weight was being lost. Many types of experiments on the energy balance had, in fact, been performed, and the information to be derived from these studies seemed greater than had been recognized.

The task of finding an answer to the problem was performed in the following way. The voluminous experimental literature on obesity was studied and the data put on hundreds of cards, for easy rearrangement. It was hoped that the data could be assembled in such a way that, from the whole, a clear-cut picture of the nature of obesity would emerge. Much of the experimental data, at first glance, appeared to be contradictory; but it was recognized that if integration of the material were achieved by the expedient of leaving anything out, the result would be correspondingly diminished in value. From time to time, as the material was studied, some pattern or other began to emerge, but experimental findings that did not fit in with it caused structure after structure to be torn down. The process of integrating the data, involving, as it did, considerable preliminary fumbling and many fruitless attempts, extended over a number of years. Meanwhile, new material was constantly being added, necessitating continual reorganizing of the old.

In this task there was no dearth of information. The "lights of chemistry" had grown brighter since the time of Harvey, and difficulty now seemed to lie in the labyrinthine details of the intermediary metabolism that had come to light since Schoenheimer introduced the use of isotopes as tracer elements in physiological experiments. It seemed that physiology, emerging from the dark ages in which it had been necessary to "guess what was going on inside a house by observing what went in at the door and what went out through the chimney," presented more difficulties than ever. The clue of thread, however, appeared to be found in the concept of the "milieu interieur" which, originating with Claude Bernard, led to Cannon's concept of homeostasis, and from this to Rony's application of homeostasis to the problem of obesity. Reflecting upon the implications of Rony's contribution, after a second or third reading of his classic treatise (18), and pondering at the same time the intricacies of the data assembled from the work of hundreds of in-

vestigators, the concept of obesity as a compensatory process dawned on me with such clarity that I felt stupid for not having seen it before. Checking this in detail with the experimental data was then a most pleasurable task, for frustrating incongruities resolved themselves into a consistent pattern; everything fitted together like clock-work. It was, therefore, with considerable confidence that, when the occasion arose, I presented the concept of obesity to which my studies had led: *Obesity, in most cases, is a compensatory hypertrophy of the adipose tissues, providing for a greater utilization of fat by an organism that suffers a defect in its ability to oxidize carbohydrate.* (19) (20). This concept of obesity will, doubtless, strike many as strange in view of its complete departure from the usually prevailing one. Part of its strangeness, however, will be due to the newness of some of the physiological facts on which it is based. As these come to be more widely known and the matter is explored in a penetrating manner, its strangeness, I feel sure, will disappear. The essential data on which it is based have been presented elsewhere (19-23), although it has not been possible, as yet, to present the many ramifications of experimental details that it illuminates. This concept stands on its ability to fit the clinical and experimental facts of obesity in the light of modern physiological knowledge.

TREATMENT OF OBESITY WITHOUT CALORIC RESTRICTION

Twice in the past 100 years a solution of the problem of obesity has appeared, restricting carbohydrate, alone, while allowing protein and fat *ad libitum*. The first appearance of this type of treatment, that of the diet Harvey prescribed for Banting, suffered the disadvantage of lack of knowledge concerning the constitutents of certain foodstuffs, but even more than this, from lack of knowledge of physiology needed to explain it. The second appearance of this type of treatment, that of the diet Dr. Donaldson reported in clinical conferences, does not need to suffer from either of these disadvantages. The constituents of various foodstuffs are now quite well known; and advances in physiology have provided a clear explanation of the effectiveness of diets.

Investigation of the matter, furthermore, indicates that the usual treatment, caloric restriction, has no scientific basis in an understanding of the pathophysiology of obesity, but is merely a non-specific form of therapy that reduces the weight by semi-starvation.

When a calorically unrestricted diet for obesity is used, the degree to which carbohydrate must be restricted appears to vary in different individuals, according to the degree of the obesity defect. The following regimen has seemed applicable to the great majority of cases. Reasons for specific details, dietary and non dietary, have been given elsewhere (19-23).

A CALORICALLY UNRESTRICTED DIET FOR OBESITY

With this diet you follow a definite routine that is as important as the diet itself. Have a regular hour for going to bed. Set your alarm clock for eight hours sleep, never a minute more than that, and allow time for a thirty minute walk before breakfast. It is not necessary to walk fast. Set your own pace.

Breakfast, lunch and dinner are all the same type—you eat three big meals a day:

First course of each meal: One-half pound or more of fresh meat with the fat. This part of the diet is *unlimited*. You can eat as much as you want. The proper proportion is three parts of lean to one part fat, cooked weight. Most of the meat you buy is not fat enough, so get extra beef kidney fat, slice and fry it to make up the proper proportion. Good meats are roast beef, steak, roast lamb or mutton, lamb or mutton chops, boiled beef or boiled breast of lamb, fresh pork and pork chops. Hamburger is all right if you grind it yourself just before it is cooked. Season the meat with black pepper before it is cooked or use other flavoring that does not contain salt. Do not use salt nor foods containing salt.

Second course of each meal: This part of the diet is *limited*. At each meal you have a choice of an ordinary portion of any *one* of the following: potato, boiled rice, half grapefruit, grapes, slice of melon, banana, pear, raspberries or blueberries. At the end of each meal have a cup of black coffee or tea without sugar or saccharine.

Drink water as you wish, making sure to take three full glasses between breakfast and lunch and three more between lunch and dinner. Your only other beverage is the juice of half a lemon in a glass of water, if you desire it.

After the weight is normal you can test out how far you can depart from the diet without gaining weight.

Note: This diet contains no bread, flour, sugar, salt or alcohol.

SUMMARY

The history of obesity since the end of the 18th century is reviewed, with particular attention to events connected with the Banting dietary. This treatment appears to have been, originally, one in which carbohydrates were restricted but the total food intake was not restricted. Lacking a rationale, it became modified to fit current concepts; it underwent transformation into a low calorie diet in which fat was greatly restricted.

Another, more recent, diet in which carbohydrate is restricted while the total caloric intake is not restricted is presented. The rationale for this treatment is indicated.

REFERENCES

1. Beddoes, Thomas: Observations on the nature and cure of calculus, etc. London, J. Murray, 1793.
2. Wadd, William: Cursory remarks on corpulence, ed. 3. London, J. Callow, 1816.
3. Wadd, William: Comments on corpulency. London, J. Ebers, 1829.
4. Mendel, L.: Nutrition, the chemistry of life. New Haven, Yale Univ. Press, 1923. p. 23.
5. Chalmers, T. K.: Corpulence, or excess fat in the human body. London, Longman, Brown, Green, Longmanns, 1850.
6. Harvey, William: On corpulence in relation to disease. London, H. Renshaw, 1872.

7. Banting, William: Letter on corpulence, addressed to the public, ed. 4. London, Harrison and Sons, reprinted 1885.

8. Williams, L.: Obesity. London, Oxford Univ. Press, 1926. p. 143.

9. Duckworth, Dyce: Obesity: in System of Medicine, edited by Allbutt, T., New York, Macmillan, 1897. Vol. 7, pages 607-622.

10. Salisbury, J. H.: Brief statement of the so-called Salisbury plans. London, Bailliere, 1887.

11. Oertel, M. J.: Obesity: in Twentieth Century Medical Practice, edited by Stedman, T. L. Vol. 2:623-725. New York, Wood, 1895-1903.

12. Von Noorden, C.: Clinical treatises, part 9, Reduction cures and gout. New York, E. B. Treat, 1910.

13. Ebstein, W.: Corpulence and its treatment on phyisological principles. Transl. from the 6th German edition by Keane, A. H. London. H. Grevel, 1884.

14. Seé, Germaine: Du regime alimentaire. Paris. Delahaye et Lecrosnier, 1887, page 554.

15. McLester, J. S.: Protein comes into its own. J.A.M.A., 139:897-902 (Apr. 2) 1949.

16. Grafe, E.: Metabolic diseases and their treatment. Philadelphia, Lea and Febiger, 1933. p. 146.

17. Newburgh, L. H. and Johnston, M. S.: The nature of obesity. J. Clin. Invest. 8:197-312 (Feb.) 1930.

18. Rony, H. R.: Obesity and Leanness. Philadelphia, Lea and Febiger, 1940.

19 Pennington, A. W.: Reorientation on obesity, New England J. Med., 248:959-964 (Jun. 4) 1953.

20. Pennington, A. W.: Practical reducing regimens; in overeating, overweight and obesity; Proc. Nutr. Sympos. Harvard Sch. Public Health, Boston, Oct. 29, 1952. New York, Nat'l. Vitamin Foundation, 1953. p. 123-129.

21. Pennington, A. W.: Alternate approach to problem of obesity. J. Clin. Nutrition, 1:100-106, 1953.

22. Pennington, A. W.: Treatment of obesity with calorically unrestricted diets. J. Clin. Nutrition. 1:343, 1953.

23. Pennington, A. W.: Obesity: overnutrition or disease of metabolism. Am. J. Digest. Dis. 20:268, 1953.

PATHOPHYSIOLOGY OF OBESITY

A. W. PENNINGTON, M. D., Wilmington, Del.

THE WIDELY prevailing opinion that energy exchange studies have proved the absence of any metabolic defect in obesity has, for many years, relegated biochemical details of this condition to a position of minor importance. Analysis of energy exchange experiments on the basis of their evidence for or against a passive dependence of the adipose deposits on the caloric balance, however, indicates that many cases of obesity must be attributed to a metabolic defect involving the storage of body fat (1). Details of fat metabolism, therefore, can no longer be considered inconsequential. Instead, it appears that they form the necessary basis for an understanding of the pathogenesis of obesity and its rational treatment.

THE NEWER KNOWLEDGE OF FAT METABOLISM

Studies of fat metabolism during the past two decades have necessitated a startling revision of older concepts concerning the role played by fat in the body economy. Older concepts characterized the adipose deposits as a lifeless mass, accumulating from the residue of the food intake after energy needs have been met, and remaining functionally segregated from the metabolic activities of the body until called on in time of necessity. Carbohydrate was assigned a supreme position as the supplier of energy for ordinary metabolic needs, the liver being thought in some miraculous way capable of storing enough glycogen for most of the energy needs between meals. It was believed that fat could be burned in moderate amounts if assisted by the simultaneous oxidation of carbohydrate but that if care was not taken, the precarious ability of the body to burn fat would give rise to harmful products of incomplete combustion.

If some of these ideas are still current it may very well be the result of indifference concerning biochemical details that oversimplified concepts of the energy metabolism have fostered; with body weight as the criterion of the adequacy of the energy supply to the organism (2), the intermediate steps between caloric intake and outgo have probably seemed to matter very little.

It has been found that the adipose tissues constitute an essential functional link in the regular, daily metabolic activities of the body (3). They act as an energy buffer; much of the food of all types taken at meals is rapidly converted to fat and deposited in them, and deposit fat is gradually released for energy between meals (4). The fat released, furthermore, is not converted to carbohydrate before it is utilized (5). It is burned readily by the general tissues (6) and by the liver (7), without the necessity for any simultaneous oxidation of carbohydrate (8). The liver manufactures ketones as part of the normal process of fat breakdown, and the general tissues readily oxidize these for energy (8). Ten times as much of the carbohydrate ordinarily eaten may be converted to fat as is synthesized to glycogen (9); and in the postabsorptive state fat furnishes the body with 60 per cent of its energy requirements (5). Carbohydrate, far from occupying a supreme position, serves largely as a precursor of the fat that is needed by the body for its ordinary metabolic needs from day to day (10).

These details concerning the metabolism of fat have a definite bearing on the problem of obesity, for they are all intimately involved in the physiology of fat storage. Since body fat is not converted to carbohydrate, it is clear that once fat has been introduced into the body or has been formed from ingested carbohydrate or protein, it must be accounted for, almost entirely, by fat storage and fat oxidation. The storage of fat in the body must, therefore, amount quanti-

Submitted Sept. 17, 1953.

Med. Div. E. I. du Pont de Nemours and Co.

tatively to the difference between fat available from food and fat oxidized. The essential relationships can be expressed in the following equation:

fat available = fat storage + fat utilized.

In this equation fat storage may be positive or negative in sign, or may be zero. The three terms of the equation represent the rates, equated to calories per unit of time, of the processes involved. If the body were as simple as a storage tank there would be little left to consider in connection with the matter; but the body is endowed with physiological mechanisms that exert regulatory control over each of the three processes; fat available, fat storage and fat utilized.

PHYSIOLOGICAL REGULATIONS

The fat available from the diet depends, first of all, on the caloric intake, which is ordinarily adjusted to the energy needs through the mechanisms of appetite (11). Fat can be eliminated from the diet, but since fat is formed from the other foodstuffs ingested (12) fat is made available to the organism as long as any kind of food is taken.

The storage of fat in the body was formerly considered a purely passive matter of balance between fat available from food ingested and fat utilized. Knowing that the blood lipid level tends to remain constant, it seemed that an easily reversible reaction in the adipose tissues must cause fat to be deposited or mobilized, depending on a high or low blood lipid level (13). While fat storage is undoubtedly influenced in this way it is, however, regulated by active physiological mechanisms. Wertheimer has shown that active neural and hormonal mechanisms adjust the rates at which fat is deposited in the adipose tissues and mobilized from them (3). Two sets of opposing forces form a dynamic equilibrium that appears to strike a balance at a particular level of body weight, causing the organism to resist change from an established weight level and operating to restore the level when it has been changed by unusual circumstances. These forces, through their control over fat storage, exert a powerful and, at times, a dominating influence on the balance between the caloric intake and output of the individual. Thus, the body tends to conserve energy during caloric restriction and it restores its reserves through the establishment of a positive caloric balance after weight has been lost through severe illness or starvation (11).

The utilization of fat, ordinarily, appears to be chiefly by oxidation of fatty acids, but some ketones are continually formed in the liver and oxidized by the general tissues (5). The rates at which the body oxidizes fatty acids (14) and ketones (15) are influenced by the concentrations of these substances in the blood, just as the rate at which the body oxidizes glucose is influenced by the blood glucose level (16). The extent to which the body depends on fat or carbohydrate for energy is influenced by the relative proportions of these substances in the diet (17), but considerable fat is utilized, regardless of the constituents of the diet, for if it is not supplied as food the body manufactures it from carbohydrate and protein.

The physiological mechanisms that regulate the energy balance and those that regulate energy storage are integrated in such a way that, ordinarily, the caloric intake is adjusted to the caloric output at an established level of body weight. Each of the two sets of mechanisms influences the other and also displays a certain degree of flexibility, so that either the caloric balance or the level of storage can be altered in the service of the body economy as a whole. A third set of mechanisms is also integrated with these two. It makes possible an adjustment of the organism to deal with diets in which either carbohydrate or fat is predominant.

ADJUSTMENTS TO CARBOHYDRATE AND FAT DIETS

If much carbohydrate is eaten, the pancreas is stimulated to secrete insulin (18); this furthers the conversion of carbohydrate to fat and the deposition of fat in the adipose tissues (19). If much fat is eaten, the anterior pituitary is stimulated to secrete its ketogenic principle (20). This acts on the liver (21), furthering the breakdown of fat to ketones; and the resulting ketonemia is followed by mobilization of fat from adipose deposits (22). The adrenal cortex appears to cooperate with the pituitary, for it inhibits the formation of new fat (23). The hormonal responses to the ingestion of foodstuffs appear to balance the effects on fat storage of the markedly different blood lipid levels that follow the ingestion of carbohydrate or fat predominantly. On either type of diet an appropriate amount of fat is stored.

Oxidation of carbohydrate and fat, though subject to the concentrations of these substances in the blood, is also subject to hormonal influences similar to those affecting fat storage (24). In addition, they are profoundly affected by certain intermediary products that are formed during the breakdown of the foodstuffs themselves. Wertheimer has called these substances "metabolic regulators" (25). One of them, which appears to have particular importance in connection with obesity, is pyruvic acid.

Pyruvic acid is the product of the first, or glycolytic, phase of carbohydrate breakdown in the tissues of the body; when carbohydrate is oxidized it is actually the pyruvic acid that is oxidized, for pyruvic acid must first be formed. Lactic acid has received much attention in the past, but this is merely a hydrogenated form of pyruvic acid that can only be reconverted to pyruvic acid. When much carbohydrate is eaten much pyruvic acid is formed. The general tissues proceed to oxidize this, but an unoxidized residue remains, and some of this diffuses out of the cells into the blood in the form of both lactic and pyruvic acids. These are carried to the liver (26, 27). Pyruvic acid appears to be a powerful metabolic regulator. It inhibits the conversion of fatty acids to ketones in the liver (28), so that if much carbohydrate is eaten very little fat is burned in the form of ketones. This limits the total amount of energy that the body can derive from fat (5). On the other hand, if fat is predominant in the diet and carbohydrate is greatly limited, little pyruvic acid is formed. The liver then forms ketones abundantly; these are readily oxidized by the general tissues, increasing greatly the amount of energy that the body obtains from fat (5).

It can be seen that the body is abundantly supplied with regulatory mechanisms that adjust the organism to varying conditions of diet. As a consequence, most people are able to operate on either a "carbohydrate

economy" or a "fat economy" predominantly. On either, an adequate amount of energy is supplied to the tissues and a normal store of reserve energy is maintained; the appetite is balanced to the energy output, and body weight remains constant. The intricate regulatory mechanisms ordinarily work so smoothly that their existence might almost escape notice. Indeed, with attention focussed on the simple balance between caloric intake and output, as it has been for many years, it appears that the intrinsic mechanisms have often been ignored, with the result that the body has been thought to operate as simply as a storage tank.

PATHOGENESIS OF OBESITY

There appears reason to believe that a common cause of obesity is an impaired ability of the tissues to oxidize pyruvic acid. The evidence for this consists in experimental work indicating that pyruvic acid tends to accumulate excessively in the tissues of the obese.

The tissues normally are unable to oxidize all of the pyruvic acid that is formed in them from the first phase of carbohydrate breakdown (26, 27). In certain physiological circumstances such as in strenuous physical exercise, a factor limiting the oxidation of pyruvic acid is the supply of oxygen. Some of the pyruvic acid formed in the tissues then diffuses into the blood and is carried to the liver, where it is synthesized to glycogen or fat. Much of the pyruvic acid is first reduced to lactic acid, and it diffuses into the blood in this less toxic form. The blood levels of pyruvic and lactic acids both reflect the degree to which the tissues fail to oxidize the pyruvic acid formed in them from the first phase of carbohydrate breakdown. The failure to oxidize pyruvic acid can be due either to lack of oxygen or to the limitations of the tissue enzyme systems.

Evidence for an excessive accumulation of pyruvic acid in the tissues of the obese is derived chiefly from determinations of the blood lactic acid. Lichtwitz found that light muscular exercise caused an abnormal increase in the blood lactic acid of the obese, and this was confirmed by Kugelmann (29). Prodger and Dennig obtained the same results in experiments that took into account the greater energy expenditure of the obese on a given task (30). They also determined arteriovenous oxygen differences and ruled out any circulatory insufficiency that would diminish the supply of oxygen. They reported, "The high lactic acid values which we obtained, therefore, may be considered as due to disturbed intermediary metabolism, with no relationship to circulatory insufficiency." Mayer has found an excessive accumulation of pyruvic acid in the hereditary obesity of mice (32). Horwitt has found that in human diabetes the blood level of pyruvic acid is abnormally elevated after mild muscular exercise (32); and, since insulin does not prevent the rise in pyruvic acid, this finding suggests that the often suspected common denominator between obesity and diabetes is an impaired oxidation of pyruvic acid, which precedes the development of diabetes and leads only to obesity as long as the production of insulin by the pancreas remains sufficient. It seems to have become well established that a major action of insulin is to facilitate the conversion of carbohydrate to fat (10).

An abnormally increased concentration of pyruvic acid checks not only the conversion of fatty acids to ketones in the liver, but also the oxidation of fatty acids in the general tissues (14) and the oxidation of acetate (33), a late product in the breakdown of fat. Block and Kramer found that, in the concentrations they used, pyruvic acid not only inhibited the oxidation of fat but actually stimulated the formation of fat from smaller elements (34).

Pyruvic acid, a product in the breakdown of carbohydrate, and a metabolic regulator, is also an intermediary substance in the conversion of carbohydrate to fat (35). It would seem that the person who becomes obese has, first, an impairment in the capacity of the enzyme systems for oxidizing pyruvic acid. Much of the carbohydrate he eats, therefore, instead of proceeding to complete oxidation, is converted to fat. From the equation,

$$\text{fat available} = \text{fat storage} + \text{fat utilization},$$

it can be seen that an abnormal proportion of the foodstuffs ingested would be diverted to storage as excess fat instead of being oxidized for energy. The appetite, then, regulated as it is to supply the energy needs of the body, would dictate the intake of an increased amount of food to make up for the amount diverted to storage. Thus, excessive fat storage, or obesity, would be the cause of an increased appetite, rather than the result of it.

The supply of sufficient energy to the organism appears, with good reason, to be a primary biological task for which mechanisms of regulation and adjustment are abundantly provided. The intake of energy is assured by the forces that adjust the appetite to the energy needs, and steadiness in the supply of energy to the organism is made possible by the forces that regulate energy storage. In the obese these two sets of mechanisms appear to be intact; but the third set of mechanisms, which adjusts the metabolism to deal with a predominantly fat or carbohydrate type of diet, appears to have become impaired, with the result that the task of securing sufficient energy from a predominantly carbohydrate diet can be accomplished only at the expense of an abnormal increase in the storage of body fat. The development of the obese state, in fact, appears to be an adjustment of the handicapped organism, making possible a sufficient energy supply on a highly carbohydrate type of diet. This adjustment appears to progress until the excessive size of the fat deposits, through the development of forces that they bring to bear upon the biochemical equilibria, achieve compensation by making possible the utilization of more fat for energy (36). The individual, then, maintains constant though excessive weight.

The oxidation of pyruvic acid in the tissues proceeds through a number of steps, by way of an intricate enzyme system. The details of this, as they become more fully known will, it seems, make possible the isolation of the precise point at which the metabolic fault in obesity occurs. According to a recent review by Slater (37), there are several metabolic steps, involving 2-carbon molecules, that must be traversed before pyruvic acid is converted to acetyl coenzyme A, which enters

the tricarboxylic acid cycle for the final oxidation to carbon dioxide. The essential metabolic fault in obesity would seem to involve, not the first, but a succeeding one of these steps. This would be compatible with Mayer's findings in obese mice (31). Two-carbon elements would pile up in the tissues causing, in turn, a piling up of pyruvic acid with its inhibiting effect on the oxidation of fat and acetate.

THE CAUSE OF OBESITY

An impaired oxidation of pyruvic acid can arise from a number of causes. Many genetic studies indicate that obesity is often inherited (38); and these studies have been attacked with only the weakest of logical weapons. Davenport concluded from his studies that an inherited metabolic defect in obesity would often not reveal itself till age 20 or later (30). An inherited weakness of the enzyme systems might, therefore, be a cause. It might even be inferred that the human race, which subsisted for thousands of years on a diet consisting predominantly of protein and fat (40), has not completely adjusted itself to a diet containing considerable amounts of carbohydrate.

It seems possible that toxic influences can cause obesity by interfering with the enzymatic oxidation of pyruvic acid. It is of interest that arsenic, formerly used to build up the weight of undernourished individuals, has as one of its primary actions a blocking of the oxidative pathway of pyruvic acid (41). Any substance that can combine with a sulfhydryl group can inhibit the oxidation of pyruvic acid (42). This appears to include gold and other metals (41). In the days when it was customary to give series of treatments with mercury, it was known that obesity often ensued (43). Another possibility is that a low protein or even a low calorie diet, by failing to support the tissue enzyme systems, can cause impairment in them: semi-starvation has been followed by excessive weight gain in the period of rehabilitation (44). Another possibility is suggested by the finding that lipoic acid, which has been isolated from the liver, is involved in the breakdown of pyruvic acid (37); it is not known, however, just how it participates or if it is insufficient in obesity. Studies by Kriss and Smith indicate that excess salt may impair the oxidation of carbohydrate (45) to a degree that reduces the caloric expenditure of the body (46). Dehydration of the tissues, from an insufficient drinking of water, also reduces the caloric expenditure (47). Lack of physical exercise has usually been implicated in obesity on the basis of the reduced number of calories expended, but it seems possible that lack of exercise might also cause, in some cases, an alteration in the intermediary metabolism, especially at some particularly vulnerable step. There is much in connection with the oxidation of pyruvic acid that remains for future investigation. Evidence that alcohol checks carbohydrate oxidation in the liver seems to give this substance a more important role in the development of obesity than that usually assigned on the basis of its caloric content (48).

PHYSIOLOGICAL PRINCIPLES OF TREATMENT

Treatment of obesity, for many years, has been simple in theory but difficult in practice. It has been believed that caloric restriction causes the body to "draw on" its fat deposits in amounts sufficient to maintain a normal energy supply to the organism. Difficulties arising from hunger, weakness and mental depression, have been given psychiatric explanations. Analysis of energy balance studies (1) however, indicates that while theory has triumphed the patient has starved.

Part of the difficulty encountered with low calorie diets arises from the fact that while fat is being mobilized from the adipose deposits new fat is, at the same time, being formed and deposited in them; and it appears that as the weight falls below its customary level there is an increase in the rate at which new fat is formed from carbohydrate (49). The rationale on which current treatment of obesity is based has maintained an exquisite simplicity, it seems, by disregarding the powerful physiological mechanisms that regulate and adjust the organism to varying conditions. As a result, the law of conservation of energy has been applied to storage-tank concepts of physiology and has even been raised as a warning banner against further thought or investigation.

If, as there seems ground for believing, obesity develops as an adjustment that enables an impaired organism to obtain the energy it needs on a highly carbohydrate type of diet, little can be gained by opposing the physiological forces that have brought this adjustment about. Instead, it seems that efforts should be directed toward overcoming the impairment. Lacking any specific means of restoring the ability of the tissues to oxidize pyruvic acid it seems reasonable, first of all, to avoid circumstances that may impair further the enzyme systems involved. This would mean the avoidance of foods from which it is difficult to remove the arsenic used in spraying, the avoidance of salt, the avoidance of alcohol, and the avoidance of either a low protein or a low calorie diet.

The chief means available in treating obesity seems to be provided by the ability of the body to operate on a "fat economy" when its ability to operate on a "carbohydrate economy" is impaired. This appears to make possible the regulation of weight to normal on a calorically unrestricted intake of protein and fat, provided carbohydrate is sufficiently limited. Carbohydrate must be limited to a degree that will remove the inhibiting influence of pyruvic acid on ketogenesis, so that sufficient fat can be utilized for energy. The possibility of weight reduction on a calorically unrestricted diet seems to depend entirely on securing a sufficient utilization of fat; this can be aided, also, by exercise in the post-absorptive state (5).

Application of these principles appears to provide a method of treatment that makes use of the still-intact physiological mechanisms that regulate fat storage and the caloric balance. By making use of these mechanisms, instead of opposing them as is done in treatment by caloric restriction, it appears possible to treat obesity effectively without detriment to the energy supply of the organism (50).

SUMMARY

The human body appears to be endowed with physiological mechanisms that regulate 1) the energy balance, 2) energy storage and 3) metabolic adjustments to a high carbohydrate or high fat type of diet. In common obesity the first two of these appear to be intact, while

the third is impaired. Obesity appears to develop as an adjustment of the impaired organism, making possible a sufficient energy supply on a high carbohydrate diet. The metabolic defect appears to involve the oxidative pathway of pyruvic acid. Limitation of dietary carbohydrate, specifically, as the chief source of pyruvic acid, makes possible a treatment of obesity without restriction of the total caloric intake.

REFERENCES

1. Pennington, A. W.: Obesity: overnutrition or disease of metabolism. Am. J. Digest. Dis. 20:268, 1953.
2. Keys, A.: Energy requirements of adults. J.A.M.A. 142:333-338 (Feb. 4) 1950.
3. Werthmeimer, E. and Shapiro, B.: The physiology of adipose tissue. Physiol. Revs. 28:451-464 (Oct.) 1948.
4. Schoenheimer, R. and Rittenberg, D.: Deuterium as an indicator in the study of the intermediary metabolism VI. Synthesis and destruction of fatty acids in the organism. J. Biol. Chem. 113:381-396, 1936.
5. Peters, J. P.: The interrelationships of foodstuffs in metabolism. Yale J. Biol. Med. 24:48-72 (Sept.) 1951.
6. Volk, M. W., Millington, R. H. and Weinhouse, S.: Oxidation of endogenous fatty acids of rat tissue in vitro. J. Biol. Chem. 195:493-501 (Apr.) 1952.
7. Lehninger, A. L.: Lipid metabolism. Ann. Rev. Biochem. 18:191-216, 1949, pp. 203-4.
8. Stadie, W. C.: The intermediary metabolism of fatty acids. Physiol. Revs. 25:395-441 (June) 1945. p. 414, 421.
9. Stetten, D., Jr. and Boxer, G. E.: Studies in carbohydrate metabolism. I. The rate of turnover of liver and carcass glycogen studied with the aid of deuterium. J. Biol. Chem. 155:231-236, 1944.
10. Peters, J. P.: Diabetic acidosis. Metabolism 1:223-235 (May) 1952.
11. Pennington, A. W.: An alternate approach to the problem of obesity. J. Clin. Nutrition 1:100-106 (Jan.) 1953.
12. Gurin, S.: Lipogenesis. New Engl. J. Med. 248:965 (June 4) 1953.
13. Cannon, W. B.: The wisdom of the body. New York. Norton. 1932. p. 136.
14. Wertheimer, E. and Ben-tor, V.: Fat utilization in muscle. Biochem. J. 50:573-576 (Feb.) 1952.
15. MacKay, E.: The significance of ketosis. J. Clin. Endocrinol. 3:101-110, 1943.
16. Wierzuchoski, M.: Oxidation of glucose as function of its supply. J. Physiol. 90:440-464, 1937.
17. Gilmore, R. C. and Samuels, L. T.: The effect of previous diet on the metabolic activity of the isolated rat diaphragm. J. Biol. Chem. 181:813, 1949.
18. Anderson, E. and Long, J. A.: The effect of hyperglycemia on insulin secretion as determined with the isolated rat pancreas in a perfusion apparatus. Endocrinol. 40:92-97 (Feb.) 1947.
19. Stetten, D., Jr. and Boxer, G. E.: Studies in carbohydrate metabolism VI. Effects of hypo- and hyperinsulinism. J. Biol. Chem. 162:377, 1946.
20. Goldzeiher, M. A., Sherman, I. and Alperstein, B.: The fat tolerance test in pituitary disease. Endocrinol. 18:505, 1934.
21. Harrison, H. C. and Long, C. N. H.: The distribution of ketone bodies in tissues. J. Biol. Chem. 133:209-218, 1940.
22. Kartin, B. L., Man, E. B., Winkler, A. W. and Peters, J. P.: Blood ketones and serum lipids in starvation and water deprivation. J. Clin. Invest. 23:824-835, 1944.
23. Welt, I. D. and Wilhelmi, A. E.: The effect of adrenalectomy and of adrenocortotrophic and growth hormones on the synthesis of fatty acids. Yale J. Biol. Med. 23:99-111 (Nov.) 1950.
24. Russell, J. A.: Metabolic functions of the endocrine glands. Ann. Rev. Physiol. 13:327-366, 1951. pp. 331-2.
25. Parnes, I. and Wertheimer, E.: Effect of acetate on glycogen synthesis and glucose utilization in the isolated diaphragm of rats. Biochem. J. 46:517-520, 1950.
26. West, E. S. and Todd, W. R.: Textbook of biochemistry. New York. Macmillan. 1951. p. 974.
27. Baldwin, E.: Dynamic aspects of biochemistry, Cambridge Univ. Press. 1949. p. 347.
28. Geyer, R. P., Bowie, E. J. and Bates, J. C.: Effects of fasting and pyruvate on palmitic acid metabolism. J. Biol. Chem. 200:271-274, 1953.
29. Kugelmann, B.: Untersuchnungen zur Fettsucht als ein Problem intermediärer Stoffewechselstörung. Ztschr. f. klin. Med. 115:454, 1931.
30. Prodger, S. H. and Dennig, H.: A study of the circulation in obesity. J. Clin. Invest. 11:789-806, 1932.
31. Guggenheim, K. and Mayer, J.: Studies of pyruvate and acetate metabolism in the hereditary obesity-diabetes syndrome of mice. J. Biol. Chem. 198:259-265 (Sept.) 1952.
32. Horwitt, M. K., Hills, O. W. and Kreisler, O.: Lactic and pyruvic acids in the blood after glucose and exercise in diabetes mellitus. Am. J. Physiol. 156:92-99 (Jan.) 1949.
33. Consiglio, J. G., Anderson, C. E. and Robinson, C. S.: Acetate utilization in normal, fasting and pyruvate-treated rats. J. Biol. Chem. 198:525-532 (Oct.) 1952.
34. Bloch, K. and Kramer, W.: The effect of pyruvate and insulin on fatty acid synthesis in vitro. J. Biol. Chem. 173:811-812 (Apr.) 1948.
35. Brobeck, J. R.: Metabolism and Nutrition, in Textbook of Physiology; edited by Fulton, J. F., ed 16. Phila. Saunders. 1949.
36. Pennington, A. W.: A reorientation on obesity. New Engl. J. Med. 248:959-964 (June 4) 1953.
37. Slater, E. C.: Biological oxidations. Ann. Rev. Biochem. 22:17-56, 1953. p. 20.
38. Rony, H. R.: Obesity and Leanness. Phila. Lea and Febiger. 1940. p. 181.
39. Davenport, C. B.: Body build and its inheritance. Washington. Carnegie Institution of Washington Pub. No. 329, 1923. pp. 21, 154.
40. Clark, J. G. D.: Prehistoric Europe, the economic basis. New York, Philosophical Library. 1952. p. 22.
41. Stocken, L. A. and Thompson, R. H. S.: Reactions of British anti-Lewisite with arsenic and other metals in living organisms. Physiol. Revs. 29:168-194 (Apr.) 1949. pp. 171, 185.
42. Haurowitz, F.: Progress in Biochemistry. New York. Interscience. 1950. p. 284.
43. Wadd. W.: Cursory remarks on corpulence, 3rd ed. London. J. Callow, 1816. Page 74.
44. Keys, A., et al: The biology of human starvation, Vol. 1. Minneapolis. Univ. Minnesota Press, 1950. p. 126.
45. Kriss, M. and Smith, A. H.: Oxidative changes induced by a mineral deficient diet. J. Nutrition 16: 385-393, 1938.
46. Kriss, M. and Smith, A. H.: The change in total energy metabolism of rats receiving a diet deficient in inorganic constituents. J. Nutrition. 16:375-384, 1938.
47. Von Noorden, C.: Metabolism and Practical Medicine, Vol. 3. Chicago. W. T. Keener, 1907. See table at bottom of p. 702.
48. Bollman, J. L.: Liver and Bile. Ann. Rev. Physiol. 5:321-344, 1943. p. 325.
49. Brooks, C. McC.: Study of respiratory quotient in experimental hypothalamic obesity. Am. J. Physiol. 147:727-734, 1946.
50. Pennington, A. W.: Treatment of obesity with calorically unrestricted diets. J. Clin. Nutrition 1:343, 1953.

THE SOLUBILITY OF SOME SULFONAMIDES OF CURRENT CLINICAL IMPORTANCE

J. B. Ziegler, R. E. Bagdon and A. C. Shabica, Summit, New Jersey.

THE SOLUBILITY of sulfonamides and their N^4-acetyl derivatives in aqueous media has received considerable attention, especially in recent years. This interest is occasioned by the fact that this physical property may be objectively determined, and has a significant bearing on the concentration of the drug attainable in the blood and the likelihood of appearance of such untoward side reactions as crystalluria during drug therapy.

A rather large mass of data exists in the literature on the solubility of various sulfonamides. Unfortunately, however, these investigations in most instances were carried out under such diverse conditions of solvent, acidity, temperature and general experimental method that it is practically impossible to correlate the resulting data. Also, some of the newer drugs have not been adequately treated to date, and some of the older drugs studied have since become obsolete. One object of the present work, therefore, was to determine under identical conditions the solubilities of the sulfonamides in common clinical use and their N^4-monoacetyl derivatives. Another object was to determine the reciprocal effect on the solubility of the free and acetylated drugs in solutions saturated with respect to each form. The solubilities have been determined at 37° C. over a pH range including the physiologic, in normal human urine buffered at the desired pH values as solvent.

Experimental

A. *Materials.*—The following sulfonamides were included in the present study:

(1) N^1-(2-pyrimidyl)-sulfanilamide (sulfadiazine),

(2) N^1-(4-methyl-2-pyrimidyl)-sulfanilamide (sulfamerazine),

(3) N^1-(4, 6-dimethyl-2-pyrimidyl) - sulfanilamide (sulfamethazine),

(4) a mixture of equal parts by weight of sulfadiazine, sulfamerazine and sulfamethazine (triple sulfa).

(5) N^1-(2, 6-dimethyl-4-pyrimidyl) - sulfanilamide (sulfisomidine. Elkosin), and

(6) N^1-(3, 4-dimethyl-5-isoxazolyl) - sulfanilamide (sulfisoxazole).

These materials were of clinical grade and were used as obtained from the manufacturers.

The N^4-monoacetyl derivatives were all prepared in this laboratory by chemical methods known to give authentic preparations. The chemical synthesis used to obtain these derivatives is of considerable importance in certain instances, for reasons which will be brought out later in the discussion. The melting points and empirical composition of the N^4-monoacetyl derivatives as used in this work are listed in Table I.

Research Department, Ciba Pharmaceutical Products, Inc.

Submitted Sept. 18, 1953.

TABLE I

Acetyl Derivative of:	Melting Point °C.		Composition %C	%H	%N
sulfadiazine	262-263 d.	Calcd.*	48.56	4.25	18.88
		Found	48.63	4.56	18.74
sulfamerazine	249.5-253	Calcd.	50.97	4.61	18.29
		Found	50.95	4.89	18.27
sulfamethazine	248-250	Calcd.	52.48	5.03	17.49
		Found	52.61	5.28	17.56
sulfisoxazole	208-210 d.	Calcd.	50.56	4.89	13.58
		Found	50.63	5.13	13.53
sulfisomidine	310-315 d.	Calcd.	52.48	5.03	17.49
		Found	52.13	5.33	17.23

*for substance containing ¼ mole of water of crystallization per mole of sulfonamide.

B. *Method*—The solvent used was normal human urine which was buffered at the desired pH values by making use of the appropriate Clark and Lubs buffer mixtures (1) made up in urine instead of water. These solutions were used immediately after preparation in order to minimize hydrolysis of urea to ammonia, especially at the higher pH values.

An excess of the particular sulfonamide, or mixture of sulfonamides, over the amount required to give a saturated solution was placed in an ampule together with an appropriate amount of buffered urine. A series of such ampules were sealed and the mixtures were brought to equilibrium by means of a rotating rack immersed in a water bath maintained at 37° C. ± 1° C., the ampules being tumbled end-over-end. After agitation for 20-24 hours, the ampules were removed from the bath serially, opened, and the contents filtered rapidly through sintered glass funnels, using slight suction in order to minimize losses of solvent by evaporation. The pH of the filtrate was determined in a Beckman pH meter, and, in the case of the free sulfonamides, the concentration of drug was determined directly by the spectrophotometric method of Druey and Oesterheld (2). In the case of the acetylated sulfonamides, the necessary prior hydrolysis was conducted in alkaline solution, essentially according to the method of Biamonte and Schneller (3). For determinations involving mixtures of free and acetylated drugs, the concentration of the free component was determined directly from an aliquot of the original saturated solution. A second aliquot was then hydrolyzed and the total concentration of free plus acetylated drugs was determined; the concentration of acetylated drug was then found by difference. A standard solution of each sulfonamide was used in the assay of that particular drug; the appropriate correction factor was used in the assay of the acetylated drugs in order to com-

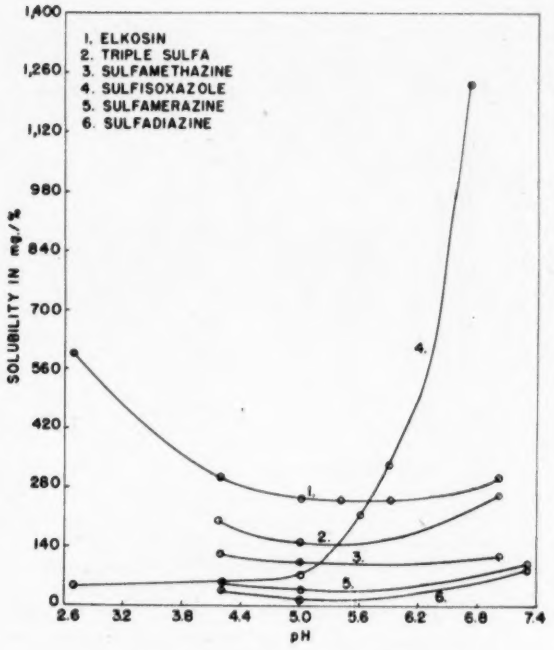


Fig. 1: Solubility of Free Sulfonamides.

pensate for the difference in molecular weights between the sample and the standard.

As stated previously, the triple sulfa was prepared by intimately mixing equal weights of sulfadiazine, sulfamerazine and sulfamethazine. Similarly, the acetyl triple sulfa was prepared by mixing equal weights of the individual acetyl sulfonamides. In the triple sulfa assays, sulfamerazine was used as the standard since the molecular weight of this sulfonamide represents the average of the three. The chromogenicity of these three drugs was found to be essentially the same on a molar basis.

In determinations involving acetyl sulfonamides the assumption was made that hydrolysis during the equilibration period was negligible. This was found to be the case by Biamonte and Schneller (3) under similar experimental conditions.

Discussion

A. *General.*—The solubilities of a number of the sulfonamides treated in this work have been determined previously, some of them by several investigators, (see, for example, references 3, 4, 5, 6, 7). While there is some general agreement among investigators as to the order of magnitude of the solubilities of certain drugs, yet there are also numerous serious discrepancies. The experimental conditions used by the various workers have in general been so exceedingly diverse, and in a number of instances so poorly defined, that it is virtually impossible to discern the reasons for these discrepancies. In several instances authors have given little, if any, indication of or evidence for the source, identity and purity of their materials. An example of the importance of this factor may be cited. We have shown (8) that, depending upon the conditions of acetylation of the parent sulfamethazine, two different acetyl derivatives may be obtained, namely an N^4-monoacetyl and an N^1, N^4-diacetyl derivative. We have found the diacetyl derivative to be very sparingly soluble, even in alkaline solution, whereas the monoacetyl derivative was the most soluble of any tested. These two compounds have identical numerical melting point values, but the diacetyl derivative melts with decomposition. Our values for the solubility of the N^4-monoacetylsulfamethazine appear to be the highest of any recorded, and it may be of some significance that literature values for the solubility of this substance show some of the greatest discrepancies. In another connection it is also worthy of note that a literature report (9) has cited cases of serious crystalluria attendant upon the clinical use of sulfamethazine. It is possible that under certain circumstances sulfamethazine may be converted *in vivo* into the very sparingly soluble diacetyl derivative. It would be difficult to account for these cases if only the solubility of the N^4-monoacetyl derivative were taken into account. These same authors have also reported that the degree of acetylation of sulfamethazine *in vivo* is extremely high (up to 74% in blood and 93% in urine).

B. *Free Sulfonamides.*—These values are given in Table II and are presented graphically in figure 1. It can be seen that the sulfapyrimidines form one broad solubility class which is characterized by a relatively small change in solubility over the pH range 4-7 and by a point of minimum solubility at about pH 5.0-5.5. Within this class two rather indistinct groups may be discerned, namely a relatively more soluble (sulfisomidine, triple sulfa, sulfamethazine) and a relatively less soluble group (sulfamerazine, sulfadiazine). The exact position of sulfamethazine as regards these two groups depends upon the pH. Sulfisomidine is clearly the most soluble drug of the entire sulfapyrimidine class in the pH range 4-7.

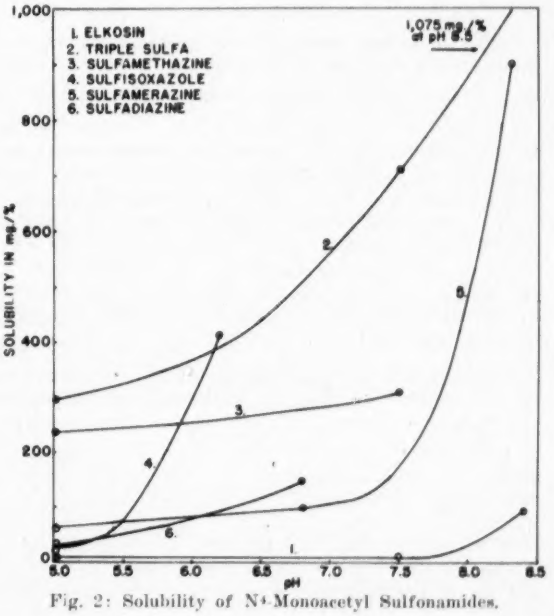


Fig. 2: Solubility of N^4-Monoacetyl Sulfonamides.

TABLE II

SOLUBILITY OF SULFA DRUGS AND N^4-ACETYL DERIVATIVES

Drug	Form		Solubility (mg. %)[2] pH 3-4.2	pH 5.0-5.1	pH 5.4-5.9	pH 6.0-7.5	pH 8.3-8.5
Sulfisomidine			593 (2.7)		246 (5.4)		
		free	300 (4.2)	254 (5.0)	247 (5.9)	302 (7.0)	
		acetyl		9 (5.0)		10 (7.5)	95 (8.4)
	mixture of			340		291	
	free and acetyl	Total[1]		334		288 (6.2)	
	derivatives	free		297 (5.1)		266 (6.2)	
		acetyl		43 (5.1)		25 (6.2)	
Sulfamethazine		free	123 (4.2)	104 (5.0)		118 (7.0)	
		acetyl		236 (5.0)		307 (7.5)	
	mixture of			359		323	
	free and acetyl	Total[1]		329 (5.1)		296 (6.1)	
	derivatives	free		133 (5.1)		119 (6.1)	
		acetyl		226 (5.1)		204 (6.1)	
Sulfamerazine		free	52 (4.2)	40 (5.0)		99 (7.3)	
		acetyl		64 (5.0)		99 (6.8)	900 (8.3)
	mixture of			131		155	
	free and acetyl	Total[1]		121 (5.1)		143 (6.3)	
	derivatives	free		53 (5.1)		66 (6.3)	
		acetyl		78 (5.1)		89 (6.3)	
Sulfadiazine		free	34 (4.2)	17 (5.0)		88 (7.3)	
		acetyl		28 (5.0)		148 (6.8)	
	mixture of			60		106	
	free and acetyl	Total[1]		54 (5.1)		96 (6.2)	
	derivatives	free		20 (5.1)		39 (6.2)	
		acetyl		40 (5.1)		67 (6.2)	
Triple Sulfa		free	196 (4.2)	150 (5.0)		263 (7.0)	
Mixture		acetyl		296 (5.0)		710 (7.5)	1,075 (8.5)
	mixture of			442		517	
	free and acetyl	Total[1]		409 (5.1)		474 (6.2)	
	derivatives	free		194 (5.1)		194 (6.2)	
		acetyl		248 (5.1)		323 (6.2)	
Sulfisoxazole			46 (2.7)		216 (5.6)		
		free	56 (4.2)	74 (5.0)	333 (5.9)	1,235 (6.7)	
		acetyl		24 (5.0)		414 (6.2)	
	mixture of			169		498	
	free and acetyl	Total[1]		162 (5.1)		486 (6.0)	
	derivatives	free		115 (5.1)		413 (6.0)	
		acetyl		54 (5.1)		85 (6.0)	

[1]Upper value = total expressed on an actual weight basis; viz., weight of acetyl + weight of free drug.

Lower value = totals expressed as free drug.

[2]The pH column headings denote the order of magnitude at which the various determinations were made. The figure given in parentheses after each solubility indicates the actual pH at which the particular determination was made.

On the other hand, sulfisoxazole (containing the isoxazole instead of the pyrimidine ring system) belongs to an entirely different solubility class; it is characterized by an extremely high solubility at pH 7 with a very rapid fall to a relatively very low value at pH 5. Furthermore, as the pH falls below 5 the solubility of sulfisoxazole continues to decrease and is still falling at about pH 2.6; this is in sharp contrast to the sulfapyrimidines where the solubility begins to increase below pH 5.

Sulfisoxazole has been rather widely considered to be a "soluble" sulfonamide. However, as Biamonte and Schneller (3) have rightly stressed, the solubility of sulfisoxazole is superior to that of the more soluble group of sulfapyrimidines (as previously defined) only in the *upper* reaches of the physiologic range of urinary pH. Thus, according to our data, sulfisomidine is actually more soluble than sulfisoxazole up to about pH 5.7; triple sulfa is more soluble up to about pH 5.4, and sulfamethazine is more soluble up to about pH 5.2. Biamonte and Schneller (3) have also stressed the noteworthy fact that urinary pH values in the *lower* portion of the physiologic range are characteristic of many diseased states.

C. *N^4-Monoacetyl Sulfonamides.*—These values are listed in Table II and are presented graphically in figure 2. Acetyl triple sulfa is the most soluble sulfapyrimidine derivative over the pH range 5-7. Acetyl sulfamethazine is quite soluble and acetyl sulfamerazine and acetyl sulfadiazine are sparingly soluble over this range. Acetyl sulfisomidine is characterized by an extremely low solubility. The degree of acetylation of sulfisomidine *in vivo* has been shown (4, 10, 11) to be relatively quite low, however. As a class, the acetyl sulfapyrimidines show only a relatively slight solubility change from pH 7 to 5. On the other hand, acetyl sulfisoxazole shows a very rapid fall in solubility from pH 6.3 to 5.

D. *Mixtures of Free and N^4-Monoacetyl Sulfonamides.*—It has been found previously (11) that N^4-

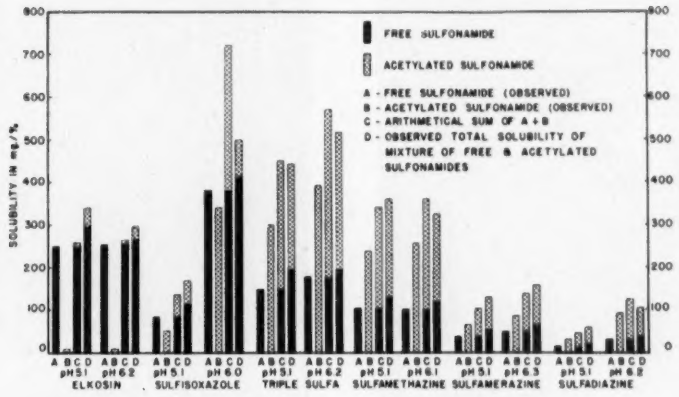


Fig. 3: Total Solubility of Mixtures of Free and N^4-Monoacetyl Sulfonamides.

monoacetyl sulfisomidine is more soluble in a saturated solution of sulfisomidine than in aqueous medium containing no sulfisomidine. It was felt to be of interest to extend this work to the other sulfonamides treated in this study at pH values of around 5 and 6. The results are given in Table II and are presented in graphical form in figure 3. Biamonte and Schneller (3) have assumed that the solubilities of the free and acetylated sulfonamides are additive in mixtures of the two. However, our results invariably showed a mutual influence of a saturated solution of each form on the solubility of the other. The solubility of the free drug was always increased somewhat in the presence of the acetyl form. The solubility of the acetyl form was sometimes increased and sometimes decreased in the presence of the free drug. The solubility of acetyl sulfisomidine was increased by a multiple of 3-4. In general, at pH 5 the solubilities of the more soluble substances (acetyl triple sulfa and acetyl sulfamethazine) were somewhat depressed in the presence of the free drug, while the solubilities of the less soluble substances (acetyl sulfisoxazole, acetyl sulfisomidine, acetyl sulfadiazine, and acetyl sulfamerazine) were somewhat elevated. It is especially noteworthy that the rapid rate of solubility increase of acetyl sulfisoxazole as the pH rose from 5 to 6 was strongly suppressed in the presence of the free drug, so that under these conditions the increase in this range was relatively slight. In the presence of the free drug the differences in solubility over this pH range between the acetyl derivatives of sulfadiazine, sulfamerazine, sulfisoxazole and sulfisomidine may be considered to be of little significance.

We are indebted to Mr. Louis Dorfman and his associates of the Microanalytical Group for the microanalyses recorded herein, and to Mr. Felton Davis of the Medical Service Division for helpful discussions of various aspects of this problem.

REFERENCES

1. N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 6th Ed., 1946, pp. 1102-1103.
2. J. Druey and G. Oesterheld, Helv. Chim. Acta, *25*, 753 (1942).
3. A. R. Biamonte and G. H. Schneller, J. Am. Pharm. Assn., Sci. Ed., *41*, 341-345 (1952).
4. R. Meier, O. Allemann and H. v. Meyenburg, Schwz. Med. Wschr. *74*, 1091 (1944).
5. L. H. Schmidt, H. B. Hughes and E. H. Badger, J. Pharmacol. & Exper. Therap., *81*, 17 (1944).
6. F. A. Svec, P. S. Rhoads and J. H. Rohr, Arch. Int. Med., *85*, 83-90 (1950).
7. P. S. Rhoads, C. E. Billings and V. J. O'Conor, J. A. Med. Assoc., *148*, 165-170 (1952).
8. J. B. Ziegler and A. C. Shabica, in press, J. Am. Chem. Soc.
9. W. McDermott, D. R. Gilligan, C. Wheeler and N. Plummer, N. Y. State J. Med., *44*, 394-397 (1944).
10. O. Gsell, Schwz. Med. Wschr., *74*, 1095 (1944).
11. F. Gross, H. Gysel and B. H. Ringier, unpublished observations.

PRIMARY JEJUNAL ULCER: AN UNUSUAL CAUSE FOR SEVERE ANEMIA

MICHAEL MUEHLBAUER, M. D., ALBERT KRAMER, M. D. AND BERNARD EPSTEIN, M. D., Brooklyn, N. Y.

PRIMARY JEJUNAL ulcer is relatively rare. First described in 1829 by Sestier (1), it was associated with acute peritonitis by him and later observers. In several instances, perforation of the ulcer followed trauma (12, 3, 4, 5, 6). Ebeling (7) collected 47 cases between 1927 and 1932 and reported that the upper jejunum was the seat of the lesion in most, and that perforation was the precipitating cause of symptoms in all but 7 of his cases.

From Medical Service "A," Leo Loewe, M.D. Radiological Service, Milton Wasch, M.D., at the Brooklyn Jewish Hospital.

Submitted Sept. 21, 1953.

Bleeding from the small bowel either in the form of

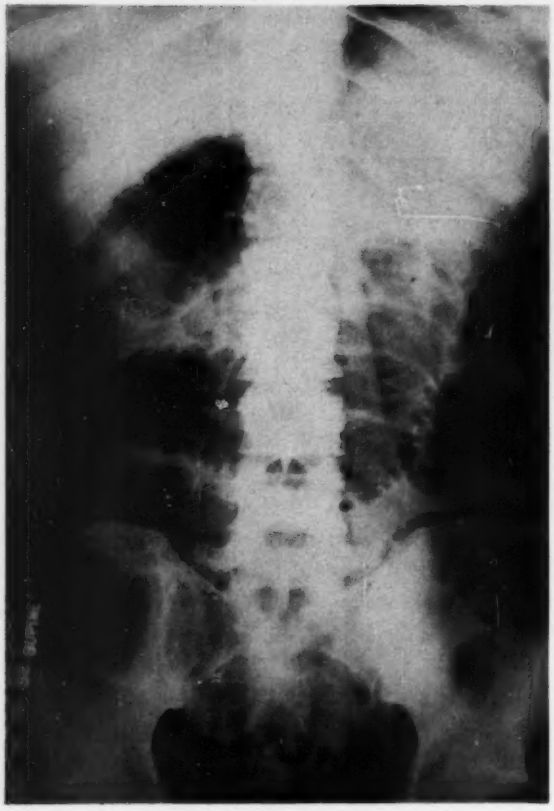


Fig. 1: Supine plain film of abdomen. There is diffuse dilatation of the lesser bowel loops in the upper and midabdomen consistent with obstruction.

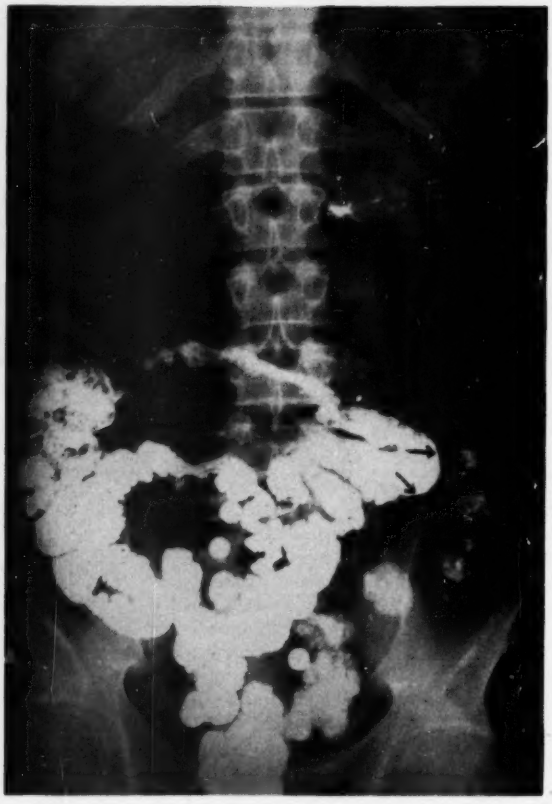


Fig. 2. A supine abdominal film four hours after a barium meal. A fixed knuckle of jejunum is present in the left lower quadrant above and medial to the left iliac crest.

severe hemorrhage with melena or gradual blood loss with secondary anemia is mentioned only infrequently. Taylor (8) described fatal hemorrhage in a 17 month old child who at necropsy was found to have an ileal ulcer associated with gastric glands of the fundal and pyloric type in the intestinal mucosa adjacent to the ulcerated area. Evert (9) was of the opinion that indications of blood loss could be detected more often if carefully investigated. Of their 45 collected cases 12 had passed grossly visible blood.

The present case of jejunal ulcer is of sufficient interest to warrant its inclusion in the literature because of the presence of persistent pain and severe anemia which remained undiagnosed until a pathological site in the distal jejunum was detected roentgenologically.

CASE REPORT

M. R., a 29 year old white male, entered the hospital for the fifth time on October 16, 1952 because of weakness and anemia. Marked pallor, weakness and mild exertional dyspnea had been present since 1943, associated with epigastric cramps, occasional nausea and anorexia. The diagnosis of chronic hypochromic microcytic anemia of undetermined origin was made at that time. On 3 subsequent admissions no other diagnosis could be established. Examinations of the stool for occult blood were occasionally positive. However, gastrointestinal roentgenograms were reported as revealing no evidence of organic disease. The anemia became so pronounced during each of two periods of hospitalization that 5 pints of blood had to be administered.

His subjective complaints for the past 10 years were mainly severe abdominal cramps which were not believed characteristic of duodenal ulcer. The pain was often present before breakfast, and occasionally awakened him from sleep. Since the patient had used lead products in his work in the past for four years as a radio mechanic, intensive studies for lead poisoning were done. Roentgenographic studies, 24-hr. urine examinations for lead after an attempt at mobilization with dihydrotachysterol, urine porphyrin determinations and blood studies were all negative.

The patient had been placed empirically on thyroid and massive doses of B-12 and folic acid on previous admissions with no change in the reticulocyte count or in the blood picture. During March 1952 he was admitted again with homologous serum jaundice following blood transfusions, but no weight loss, melena or gross hemorrhage. The hepatitis responded readily to treatment.

On his present admission physical examination revealed a markedly pale white male in no apparent discomfort. He had a pronounced reactive depression, which was attributed to his prolonged anemia and disappointment in the failure of previous therapeutic attempts. His temperature was 98.6 degrees, pulse 92 per minute, respirations 20 per minute and blood pressure 110/70 mm/Hg. His conjunctivae and mucous membranes revealed a marked pallor. Examination of the heart and lungs revealed no abnormal findings except for a soft systolic murmur, most prominent at the apex. The liver edge was palpated two fingers below the costal margin in the mid-clavicular line. No clubbing of the fingers or toes was observed. Rectal examination revealed a normal prostate; stool on the gloved finger was brown.

Laboratory studies on admission revealed an initial hemoglobin of 27% with a red blood count of 2.95 million, white

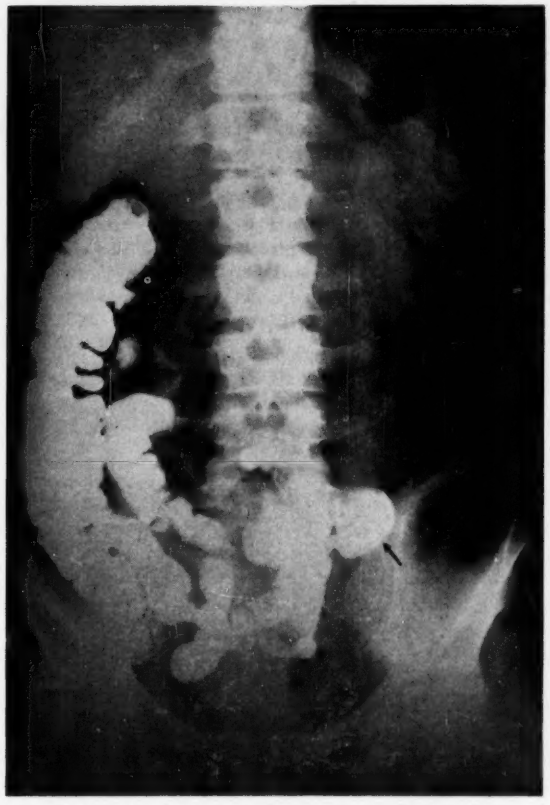


Fig. 3. Supine abdominal film five hours after a barium meal. This study was made one hour later than Fig. 2. The fixed loop of jejunum can again be seen just above the left sacroiliac joint.

blood count 14,500 with 82% polyps, 15% lymphs, 2% eos., 1% baso. Urinalysis was negative as was the Mazzini. Blood chemistries all were within normal limits except for the serum iron which was .04 mgms.% with a normal of .10 mgms.%. Hematologic survey revealed hypochromic microcytic cells with evidence of anisocytosis and poikylocytosis, and normal platelet distribution. Bone marrow aspiration disclosed an active one with no evidence of leukemia or osteosclerotic anemia. There was no evidence of hemolytic disease; studies showed normal fragility, normal fecal urobilinogen and negative findings for auto- and isoantibodies. The icterus index was normal. X-ray examinations of the long bones and skull were negative. Clotting time, bleeding time and prothrombin times were all within normal limits. Reticulocyte count was .8%. To rule out the sprue-like syndrome, despite the absence of a megaloblastic anemia, a vitamin A tolerance test as well as an oral glucose tolerance test was performed and found to be normal. Gastric analysis revealed free hydrochloric acid. Stool examination for ova and parasites was negative. Repeated stool examination for occult blood via the Guaiac test revealed a one plus, one plus, four plus, four plus, four plus, three plus, four plus result on unrestricted meals. Sigmoidoscopy revealed a pale mucosa but no lesions. Barium enemas with air contrast studies were then performed and were negative. Gastroscopic examination showed only pale mucous membranes. Directed by the frequent finding of occult blood in the stools emphasis was given to the radiological examination of the small bowel. Repeated and detailed studies were reported by one of us (B. S. E.) as disclosing that, "In the distal jejunal coils one can demonstrate what appears to be a constant deformity in the loop of the bowel. This can be demonstrated on two different occasions. While the deformity is not typical of any specific lesion one cannot escape the fact that there is a definite irregularity,

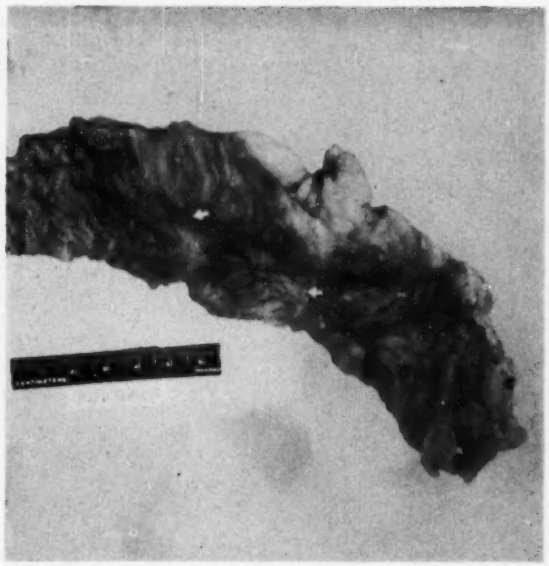


Fig. 4: (a) The resected portion of jejunum revealing two ulcers, one 2.5 cm in diameter, the second 1.2 cm in diameter.

moderate distention and partial delay in the passage of barium through the loop of bowel. Hence the probability of organic disease in this area is most likely. After 5 hrs. some barium is still retained in the distended loop of the jejunum." The diagnosis of a probably benign constricting lesion of unknown origin was made and a laparotomy performed on November 16, 1952. About 8 feet proximal to the ileo-cecal junction at the distal end of the jejunum an indurated cicatrizing area was found which formed a constricting ring and produced a widened segment above the area. Ten inches of jejunum were resected and primary anastomosis was performed.

Pathologic examination of the specimen revealed two ulcers, one 2.5 cm in diameter, the second 1.2 cms. in diameter. The bases of the ulcers were tan brown, glistening and moderately soft, and the walls were raised 0.2 cms. above the surface and were moderately soft. Microscopically, one preparation showed normal mucosa at both ends and in the midportion the mucosa was completely denuded. The base was formed by dense fibrous tissue infiltrated with many inflammatory cells. In another preparation extravasated blood was seen between the mucosa and the muscular coat. Extravasation of blood was also noted in the serosa. The pathologic diagnosis was simple benign jejunal ulcers, chronic.

The patient made an eventful recovery. He has been followed since periodically. His hemoglobin has been maintained at about 100% and the stool has remained constantly negative for occult blood. Gastrointestinal series and small bowed study on January 30, 1953 demonstrated a perfectly normal functioning gastrointestinal tract. The patient has now resumed normal activities and is back to work.

DISCUSSION

Primary ulcers of the small intestine have been reported mainly in association with acute spontaneous perforation and peritonitis, perforation after trauma, intestinal obstruction and more rarely unexplained melena (10, 11). Cases of perforation of simple ileojejunal ulcers were described by G. Balice (12), Buckstein (14), and M. Russo (13). Wilson (16) reported an instance of melena in a patient demonstrating heterotopic gastric mucosa in the ileum. This patient required hospitalization after two bouts of dark red

Fig. 4: (b) Microscopically, the preparation shows normal mucosa at the end of the ulcer, and in the mid-portion the mucosa is completely denuded. The base is formed by dense fibrous tissue infiltrated with many inflammatory cells.

blood passed per rectum, massive in nature. At laparotomy (18 inches from the ileo-cecal junction), 3 constricting rings reduced the diameter of the ileum to about one-half the normal; eight inches of ileum was resected. The microscopic pathologic report revealed simple ulceration containing gastric mucosa associated with congenital stricture.

In our case some of the known and described complications were present. More outstanding was the presence of an insidious, severe anemia which lasted for ten years. All of the indications for profound and protracted blood loss were there, and the only treatment available was replacement therapy, since no bleeding lesion could be determined. While it is true that there was never melena nor passage of red blood, yet a chronic anemia of such degree could establish itself through the more or less constant seepage from an ulcerated area in the distal end of the jejunum. The only indication of this was the presence of occult blood. We wish, therefore, to stress the importance of thinking of the possibility of primary ulcers of the small intestines in patients who present themselves with anemia due to blood loss from the gastrointestinal tract, a nondescript type of dyspepsia and pain around and below the umbilicus lacking the periodicity and rhythmicity of duodenal ulcer. If the investigation does not disclose lesions in either the esophagus, stomach or colon, the small intestines should be carefully investigated roentgenologically.

The roentgenological demonstration of primary ulcers of the jejunum and ileum is difficult, and the appearance of a typical niche is observed only in rare instances. Evert et al (9) report that in their two cases, recognition of ulcers by barium meal was possible mainly due to the presence of constricting signs. Buckstein (14) describes a case of a 52 yr. old man in which a niche-like projection in the involved area of the upper jejunum was present but recognized as such only after perforation had taken place and at operation found to be the site of the perforation. A similar case is reported by Harris (15) who demonstrated a niche-like projection in the left upper quadrant which was interpreted to belong to the posterior wall of the stomach. Perforation, however, occurred and the niche was found to be a primary jejunal ulcer. Since the demonstration of a niche is rarely possible, emphasis should be placed on other results of ulceration. These include constriction due to cicatrization with or without dilatation proximal to the constricting area, and retention of barium in such a segment. The change or disappearance of typical mucosal markings in a segment that might be only slightly narrowed may be due to the inflammatory changes within the segment of the gut.

SUMMARY

A case of unexplained anemia of 10 yrs. duration is presented. Although all evidence led to the gastrointestinal tract as the site of blood loss, the jejunum was not implicated until the 5th admission to the hospital. A summary of the diagnostic aides from the standpoint of history, laboratory and roentgenology is given in attempting to establish the diagnosis preoperatively.

REFERENCES

1. Sestier, A.: Perforation du jejunum ayant pour cause une peritonite aigue. Bull. Soc. anat. de Paris 4:33, 1829.
2. Wagner, E.: Fall von perforierendem Geschwuer im Anfange des Jejunums, Schlag auf die untere Koerperhälfte, Ruptur der Niere, Peritonitis, Tod. Arch. F. physioiog. Heilkunde, N. S. 2:280, 1858.
3. Taylor, A. S.: Cases and Observations in Medical Jurisprudence. Death from perforation of the jejunum as a result of disease, death apparently as a result of violence. Guy's Hospital rep. 11:282, 1865.
4. Reveredin, J. L.: Perforation du jejunum-peritonite subaigue-Mort: autopsie. Bull. Soc. Anat. de Paris, 42:597, 1867.
5. Brigidi, N.: Larghe Ulcere Croniche Nel Tenue intestino, grazz. d. osp. M:1050, 1893.
6. Dodson, A. E.: Death from rupture of intestinal ulcer. Brit. M. J., 1:718, 1906.
7. Ebeling, W. W.: Primary jejunal ulcer. Ann. Surg. 97:851, 1933.
8. Taylor, A. L.: The Epithelial heterotopias of the alimentary tract. J. Path. and Bact. 30:415, 1927.
9. Evert, J. A., Black, B. M. and Docherty, M. B.: Primary non specific ulcers of the small intestine. Surgery 23:185. 200 Feb. 1948.
10. Bockus, H. L.: Gastroenterology, Vol. II, p. 146.
11. Berry, C. H. and Dailey, U. G.: Primary Ulcers of the Jejunum. Am. J. Digest. Dis. 7:63, Feb. 30.
12. Balice, G.: Perforation of simple ileo-jejunal ulcers with report of a case. Gion Ital, Chron. 3:665-72, Oct. 47.
13. Russo, M.: Subacute solitary ulcers with perforation of the ileum. Case Report. Pathology 39:200-03, July-Aug., 1947.
14. Buckstein, J.: Primary ulcer of the small intestines—The Digestive Tract in Roentgenology, 37:461, 1948.
15. Harris, J.: Primary Jejunal Ulcer, a case report, Radiology 26:497, 1936.
16. Wilson, E.: Melena from heterotopic gastric mucosa in the ileum. Lancet 2:855-856, Dec. 23, 1950.

CLINICAL COMPARISON OF FOUR ANTICHOLINERGIC DRUGS

JACOB A. RIESE, M. D.*, West New York, N. J.

WITHIN THE last four years there has been a growing volume of medical literature detailing the therapy of peptic ulcer with various new anticholinergic drugs. Reported results suggested that among these might be found the nearest to the ideal vagal blocking agent which would combine efficacy with prompt pain relief, minimal side effects and roentgenologically-proved ulcer healing.

A study to evaluate these different proprietary formulations was performed on 46 patients with peptic ulcer. This study was undertaken at the Gastro-Intestinal Clinic of Jersey City Medical Center.

METHOD

Four vagal blocking agents were evaluated: Banthine, Prantal,* Antrenyl, and a coded preparation, Drug A.

Our 46 cases were composed of the following clinical entities:

Duodenal ulcer	34 patients
Gastric ulcer	4 patients
Hypertrophic gastritis & Duodenitis	1 patient
Jejunal ulcer	4 patients
No organic pathologic condition	3 patients

Diagnosis in each case was established from comprehensive history, physical examination and roentgenographic studies. All patients had complained of pain, including those 3 cases which we have tabulated as having "No organic pathologic condition."

Regimen of treatment consisted of therapy with an anticholinergic drug for a minimum period of one month, although most courses were continued for much longer periods. Each patient received courses of treatment with at least two of the cholinergic blocking agents. The majority of patients eventually received all four of the preparations being tested (Table I).

TABLE I

COURSES OF THERAPY

Diagnoses	No. Cases	Number of Patients Treated with Banthine	Prantal	Antrenyl	Drug A
Duodenal ulcer	34	16	21	10	10
Gastric ulcer	4	4	4	4	4
Jejunal ulcer	4	2	4	3	0
No organic pathological condition†	4	2	0	0	2
Totals	46	24	29	17	16

†Includes one case hypertrophic gastritis and duodenitis.

Banthine was administered in dosage of 1 tablet (50 mg.) q.i.d.

Prantal was administered in dosage of 1 or 2 tablets (100-200 mg.), q.i.d.

Antrenyl was administered in dosage of 1 or 2 tablets (5-10 mg.), q.i.d., usually the latter dosage.

Drug A was administered in dosage from 5-100 mg.

*Senior attending physician in charge, Gastrointestinal Clinic, Jersey City Medical Center.

Results were judged clinically by relief from pain. Patients were questioned and examined for evidence of atropine-like side actions.

RESULTS

Pain Relief: Graded from "No Relief" through 1 plus, 2 plus, 3 plus and 4 plus. The last indicates complete relief.

TABLE II

	No. Cases	No Relief	1+	2+	3+	4+	% 4+ Relief
Banthine	24	1	3			20	83%
Prantal	29					29	100%
Antrenyl	17	3	1	2	1	10	59%
Drug A	16	6	5	3		2	12.5%

Prantal: 29 patients (100%) had 4+ (complete) pain relief.

Banthine: 20 patients (83%) had 4+ (complete) pain relief. 1 had no relief.

Antrenyl: 10 patients (59%) had 4+ (complete) pain relief. 3 had no relief.

Drug A: 2 patients (12.5%) had 4+ (complete) pain relief. 6 had no relief.

SIDE EFFECTS

Patients were questioned as to side effects. Replies included all the well known complaints of dryness of the mouth, blurring of vision, constipation, and urinary difficulties of various types with bladder discomfort.

One 70 year old patient, a case of benign gastric ulcer of 20 years duration with deformity of the stomach due to scarring, also had definite prostatic hypertrophy. He has been maintained on Prantal (1-2 tablets q. 6 h.) with complete relief of pain and no urinary retention. This case contrasted dramatically with other elderly males with prostatism who suffered acute retention while being treated with Banthine.

With the dosage employed (200 mg. daily) practically all patients taking Banthine experienced severe (4+) atropine-like side actions.

In contrast, no side actions occurred with Prantal, even at daily dosages up to 800 mg.

Generally, patients taking Antrenyl (20-40 mg.) daily, had mild or 1+ side actions.

No side actions occurred with Drug A. (See Table III).

TABLE III

COMPARATIVE SIDE ACTIONS

Drug	Side Actions
Banthine	Severe (4+)
Prantal	None
Antrenyl	Mild (1+)
Drug A	None

DISCUSSION

Many investigators have published reports on various aspects of peptic ulcer therapy with Prantal (1-16). There is almost universal agreement as to its effectiveness, prompt pain relief and absence of side actions. In the statistically significant number of patients encompassed in these reports, there were only isolated instances of drug withdrawal because of side effects. Our experience with the 46 cases reported here confirms these observations.

Banthine has resulted in multiple side actions. Discomfort has been such that drug withdrawal has been necessary in up to 20% of cases (17-24, 27, 28). Our observations, especially in elderly males with prostatism, have underlined the objectionable urinary retention that follows use of Banthine in these patients. These side actions occurred at a minimum dosage level of 50 mg. q.i.d.— a therapeutic level thought by some investigators to be inadequate. Obviously, at higher dosage levels, side actions would be much more pronounced.

Antrenyl has been introduced recently. Mattman and Strutner (25) in a preliminary report noted: "Oral Antrenyl resulted in more symptomatic relief than belladonna, but its side effects are more pronounced." In comparing intramuscular Antrenyl with atropine, they noted toxic side effects of both drugs to be of similar magnitude. The side effects we encountered with Antrenyl, however, were mild when compared with Banthine side actions, but were more marked than those occurring with Prantal. Rowen *et al.* (26) reported on Antrenyl in a comprehensive paper: "In clinically effective dosage, Antrenyl causes side effects, principally dryness of the mouth, in almost all patients. A number of patients experienced effects on the central nervous system such as dizziness, drowsiness, mental confusion, and nervousness after administration of Antrenyl. Despite the occurrence of hesitancy of urination, no evidence of renal damage was encountered in our series."

Patients who had received both Banthine and Prantal, unequivocally preferred Prantal. Eight patients who had been treated with regular Prantal were given tablets of Prantal with Phenobarbital (gr. ¼).*

In five cases Prantal with Phenobarbital has been as efficient as regular Prantal when given twice daily instead of the previous four times daily. In an additional three cases, Prantal with Phenobarbital was more efficient in affording complete pain relief than when regular Prantal alone was administered.

In 23 cases Prantal Repeat Action Tablets* were substituted for regular Prantal. Prantal Repeat Action was as effective as regular Prantal in the excellent results obtained. The obvious advantage of this repeat action principle is the longer effectiveness of action, resulting in less frequent medication.

SUMMARY

Forty-six peptic ulcer patients were treated in successive courses with four anticholinergic drugs: Banthine, Prantal, Antrenyl, and a code preparation, Drug A. Clinical trial was given to each medication for periods of one or more months.

Clinical evidences of relief of ulcer pain and of side actions were recorded and compared.

Prantal was the most effective and best tolerated anticholinergic. Prantal provided complete pain relief in all subjects without side actions. No side actions occurred even at a dosage level of 800 mg. daily. Prantal with Phenobarbital (gr. ¼) and Prantal Repeat Action Tablets were also found effective.

Banthine resulted in pain relief in 88%. However, atropine-like side actions were marked in all patients.

Antrenyl resulted in pain relief in 49%. Side actions occurred in all patients but were milder than those resulting from Banthine.

Drug A resulted in pain relief in 2 of 16 patients. No side actions occurred.

CONCLUSIONS

In our experience, using ulcer pain relief and absence of atropine-like side actions as criteria, Prantal proved to be the most effective and best tolerated anticholinergic drug of the four preparations tested in this study.

BIBLIOGRAPHY

1. D'Imperio, F.: Prantal methylsulfate in gastrointestinal diseases, a study of 25 cases. J. M. Soc. New Jersey *50*:265 (June) 1953.
2. Hawkins, G. K., Margolin, S. and Thompson, J. J.: Gastric emptying time: comparative studies with placebos, Prantal and Banthine. Gastroenterology *24*:193 (June) 1953.
3. Heineken, T. S.: Peptic Ulcer—A New Advance in Therapy, Scientific Exhibit, Medical Society of New Jersey meeting, Atlantic City, May 19-20, 1952.
4. Heineken, T. S.: A new cholinergic blocking agent in the treatment of duodenal and gastric ulcers: a preliminary report. Am. Pract. & Digest. Treat. *3*:701 (Sept.) 1952.
5. Heineken, T. S.: Scientific Exhibit at National Gastroenterological Association meeting, Oct. 21-24, New York, 1952.
6. Heineken, T. S.: An evaluation of Prantal in ulcer management: follow-up of preliminary report. Rev. Gastroenterol, *20*:829, Nov., 1953.
7. Hoffmann, C. R.: A clinical evaluation of diphenmethanil methylsulfate in the treatment of peptic ulcer disease. Am. J. Digest. Dis. *20*:45 (Feb.) 1953.
8. Margolin, S., Doyle, M., Giblin, J., Makovsky, A., Spoerlein, M. T., Stephens, I., Berchtold, H., Belloff, G. and Tislow, R.: Pharmacological properties of a new parasympathetic blocking agent, N,N-dimethyl-4-piperidylidene-1,1 diphenylmethane methylsulfate (Prantal). Proc. Soc. Exper. Biol. & Med. *78*:576, 1951.
9. Marks, J. A.: Prantal Methylsulfate—a new anti-

cholinergic drug for the treatment of peptic ulcer, New York State J. Med. *52*:1783 (July 15) 1952.

10. McHardy, G. and Browne, D. C.: Clinical appraisal of gastrointestinal antispasmodics. South. M. J. *45*:1139 (Dec.) 1952.

11. Perlman, P. L. and Bonsal, C.: Metabolism and excretion of the parasympathetic blocking agent, N,N-dimethyl-4-piperidylidene-1, 1 diphenylmethane methylsulfate (Prantal) in dogs. J. Pharmacol. & Exper. Therap. *105*:357 (Dec.) 1951.

12. Rowe, C. R., Jr., Grimson, K. S. and Flowe, B. H.: Study of a new quaternary ammonium derivative, Prantal, capable of reducing gastric secretions and motility; tests in animals and man, trial in 44 patients with peptic ulcer. Gastroenterology *21*:90 (May) 1952.

13. Sperber, N., Villani, F., Sherlock M. and Papa, D.: A new class of parasympathetic blocking agents. J. Am. Chem. Soc. *73*:5010 (Oct.) 1951.

14. Vogel W. F.: Clinical results with Prantal Methylsulfate, a new parasympathetic blocking agent; preliminary report. J. M. Soc. New Jersey *49*:105 (March) 1952.

15. Wissmer, B.: A new anticholinergic drug for the treatment of gastroduodenal ulcer, Praxis *41*:538 (June 19) 1952.

16. Zimmer, L. Coniaris, J., Burbank, D. and Maffey, R.: Scientific Exhibit, American Medical Association Meeting, Chicago, June 9-13, 1952.

17. Abbot, F. K., Mack, M. and Wolf, S.: The action of Banthine on the stomach and duodenum of man with observations on the effects of placebos. Gastroenterology *20*:249 (Feb.) 1952.

18. Asher, L. M.: Paper read at California Medical Association Session, Los Angeles, May 13-16, 1951.

19. Benjamin, F. F., Rosiere C. E. and Grossmann, M. K.: A comparison of the effectiveness of Banthine and atropine in depressing gastric acid secretion in man and the dog. Gastroenterology *15*:727 (Aug.) 1950.

20. Kern, F., Jr., Almy, T. P. and Stolk, N. J.: An experimental and preliminary clinical study of the effect of a new quaternary amine, Banthine, upon the human colon, Gastroenterology *17*:198 (Feb.) 1951.

21. Kern, F., Jr., Almy, T. P. and Stolk, N. J.: Effect of certain drugs on the intact human colon with special reference to Banthine. Am. J. Med. *11*:67 (July) 1951.

22. Kirsner, J. B., Palmer, W. L., Levin, E. and Klotz, A. P.: Gastric antacid and antisecretory drugs: a survey based primarily on their effects upon gastric secretion in man. Ann. Int. Med. *35*:785, 1951.

23. Lepore, M. J., Golden, R. and Flood, C. A.: Oral Banthine, an effective depressor of gastrointestinal motility. Gastroenterology *17*:551 (April) 1951.

24. Longino, F. H., Grimson, K. S., Chittum, J. R. and Metcalf, B. H.: An orally effective quaternary amine, Banthine, capable of reducing gastric motility and secretions. Gastroenterology *14*:301, 1950.

25. Mattman, P. E. and Strutner, L.: Preliminary evaluation of a new drug, Antrenyl. Effect on gastric secretion, motility and results in the symptomatic care of peptic ulcer. Am. J. Digest. Dis. *20*:123 (May) 1953.

26. Rowen, B. R., Bachrach, W. H., Halstead, J. A. and Schapiro, H.: Studies on a new anticholinergic drug, Antrenyl. Gastroenterology *24*:86 (May) 1953.

27. Smith, C. A., Woodward, E. R., Janes, C. W. and Dragstedt, L. R.: The effect of Banthine on gastric secretion in man and experimental animals. Gastroenterology *15*:718 (Aug.) 1950.

28. Walters, R. L., Morgan, J. A. and Beal, J. M.: Effects of β-diethylaminoethyl xanthene 9-carboxylate methobromide (Banthine) in human gastrointestinal function, Proc. Soc. Exper. Biol. & Med. *75*:526 (July) 1950.

This study could not have been made without the aid of the Department of Gastroenterology, L. Perkel, M.D., Chief, and the following Attending Physicians to the Gastro-Intestinal Clinic, whose assistance we greatly appreciated: B. Macchia, M.D., W. Freymann, M.D., R. Horowitz, M.D., R. DeVincenzo, M.D., L. Troast, M.D., R. Lempke, M.D., L. Resnick, M.D., L. Schultz, M.D., H. Farrar, M.D. and M. Healy, R.N.

*Prantal Tablets, 100 mg., Prantal with Phenobarbital Tablets, and Prantal Repeat Action Tablets were supplied through the courtesy of the Clinical Research Division, Schering Corporation, Bloomfield, New Jersey.

Tablets of Antrenyl were kindly supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

PSEUDO-HOOKWORM: TRICHOSTRONGYLUS INFESTATION IN MAN

H. M. Spiro, 1st Lieut., MC, U.S.A., C. N. Shropshire, Capt., MC, U.S.A.F. and E. S. Fugelso, Col., MC, U.S.A., Tacoma, Wash.

MILITARY ACTIVITY in Korea has led to an increase in America of disease hitherto localized to more exotic areas. Particularly prominent has been parasitic infestation. Although *Trichostrongylus orientalis* has previously been reported in man (5, 11), and quite rarely in the United States (3, 7, 9, 12), recent observations at Madigan Army Hospital compel the suggestion that this oriental roundworm will be described more often as Korean veterans return to civil life. Its differentiation is of more than academic importance.

For some time now, there has been interest in the incidence of parasites in men returning from Korea, and it is remarkable that only when there was an awareness of the existence of *Trichostrongylus*, were such ova recognized in the stool. Here are reviewed five such cases, three soldiers and two women, native to the Japanese-Korean archipelago.

Madigan Army Hospital, Tacoma, Washington.
Submitted July 18, 1953.

Hookworm may be fancifully so designated from the truly formidable appearance of the buccal capsule:* *Necator Americanus* has two cutting plates while *Ancylostoma duodenale* has four hooks or teeth. The *Trichostrongylus*, however, presents a more amiable appearance for there are no hooks in the mouth of the worm (1). There is a striking resemblance between *Trichostrongylus* ova and those of hookworm; the

*Faust (1) (1949) points out that Goeze (1782) designated the species thusly because the bursal rays were thought, falsely, to be hooks. However, popular etymology will not have it thus.

absence of hooks in the mouth of the adult *Trichostrongylus* worm, makes the designation *Pseudo-Hookworm* irresistible. This name is peculiarly fitting since patients who have *Trichostrongylus* ova mistaken for hookworm are long and unjustly treated, without avail (3).

EPIDEMIOLOGY

Differentiation of the species of *Trichostrongylus* (of which there are said to be four) beyond the interest of the clinician, is the proper domain of the parasitologist. species are recognized by cultures of the ova or by direct study of adult worms—they have slightly different looking tails (11). The species from Korea is presumed to be *Trichostrongylus orientalis*, of length approximately 5 mm.

The overall diagnosis in endemic areas has variously been reported as ranging from 9% in India (6) to 70% in South Persia (11). The parasite is more often found in sheep raising areas. Characteristically, *Trichostrongylus* is found in sheep and goats, even in the Southern United States. Germane to the present study is a reported 25% incidence in Korean children and soldiers (2). In the front areas, where sanitation is at the worst, children and G. I.'s predominate and are often in close contact; one can easily visualize the transmission of ova from a native to the alien population. Of the few cases reported in the United States, only two are believed to have occurred in natives who have not traveled beyond the seas (3).

An intrepid experiment has been carried out by Sandground (8), who ate several larvas in order to see how long infection persisted. He had his meal in 1936; in 1946 the dauntless investigator still passed ova in his stool. Korean returnees assuredly will continue to harbor the parasite for similar periods.

No studies have been done, as far as is known, on the persistence of infection in endemic areas; the possibility of reinfestation makes such investigation most unlikely.

LIFE CYCLE

Infestation occurs through the ingestion of raw vegetables contaminated with the larvas of ova (1, 10). Unlike hookworm, *Trichostrongylus* is not acquired by the cutaneous route; one ingenious experimenter scattered *Trichostrongylus* on the floor and walked barefoot on it without, however, acquiring the disease (5). Apparently infestation occurs only through the oral route.

The eggs develop into adults in 25 days in the intestines without migrating through the lungs. Unlike true hookworm, they go through no extra-gastrointestinal migration. On one occasion, however, a single male worm was recorded, appropriately, in the vermiform appendix. The head of the adult is imbedded in the intestinal wall; the unarmed mouth of the parasite, lacking hooks, does less damage than the hookworm. Usually infestation is light and few worms are present, in contrast to the usually massive number of hookworms. In the duodenum, the adult female lays eggs which pass out, still in the egg stage, in the stool to hatch in the soil. Larval stages of *Trichostrongylus* thereafter are identical with those of hookworm. Either the larvae or the ova may be infective and close the cycle (10).

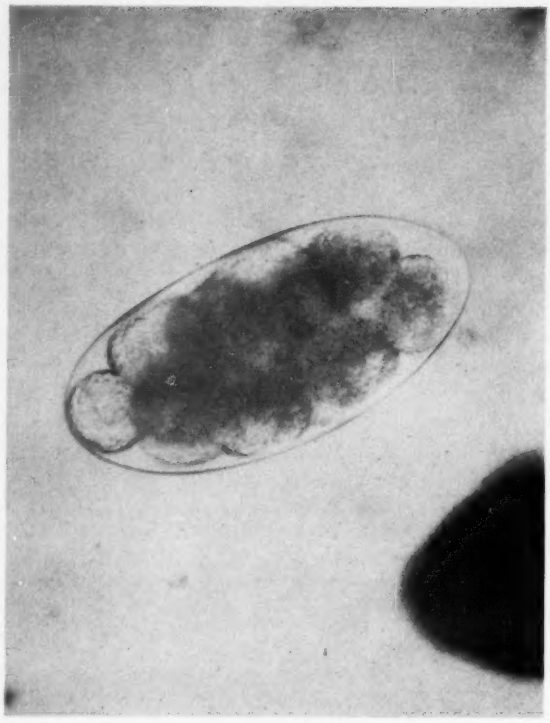
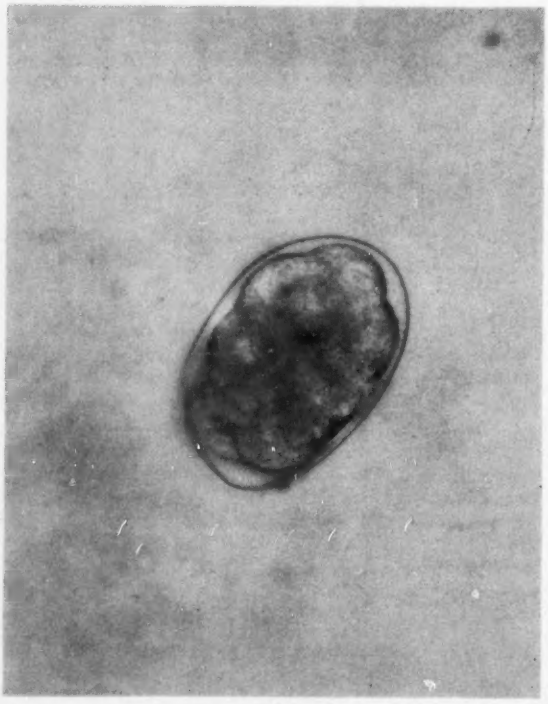


Fig. 1: (A) Trichostrongylus orientalis egg.



(B) Hookworm egg.

In the body, the worms penetrate the intestinal mucosa and cause hyperemia of the intestinal wall. Desquamation with bleeding results in a mild anemia. There is really no evidence of any but local damage (1, 10).

SYMPTOMS

Several hundred worms may be necessary to provoke clinical manifestations, which are usually correlated with the number of parasites (10). Symptoms, however, are rare; diarrhea is occasionally reported. The harmless mouth and the small size of the adults account for their relative benignity (3).

DIFFERENTIATION (1, 3, 10, 12)

The *Trichostrongylus* egg differs from the hookworm egg by being rather longer and slightly wider. Hookworm eggs measure about 64 x 41 micra while those of *Trichostrongylus* are calculated in the literature to be approximately 90 x 45 micra. The *Trichostrongylus* shell membrane is thicker and greener; possibly more characteristic are the 16 segments of the *Trichostrongylus* ovum as set against the fewer divisions (usually 1-4) found in the hookworm embryo. In the heat the hookworm embryo divides rapidly so that if the stool is allowed to sit for any great length, the hookworm egg may possess as many divisions as the *Trichostrongylus*. Fancifully, some have compared the *Trichostrongylus* egg in shape to a hen's egg, to a seedless grape, or to an elongated persimmon. A picture is appended from which the reader may draw his own fancies.

CLINICAL COURSE

It would be gratuitous to review the present cases in great detail. They are presented to make physicians aware of the problems and are summarized briefly below. Certain points, however, demand comment.

None of the patients had symptoms related to infestation with *Trichostrongylus*, so that the discovery of the worms was purely fortuitous and related to an investigation of the incidence of parasites in the general returned population. Eosinophilia was a guide, however, and was significant in the two Japanese women with endemic disease; that their stools were persistently positive postulates a more massive infestation over many years of exposure. Case 4, in whom the ova was demonstrated only once, had a marked eosinophilia, but the rise and fall in eosinophiles correlated with the persistence and then the eradication of an accompanying *Trichuris trichiura*. That the two women and Case 5, who resided in the Philippines and in Japan (though unwillingly) for some years, had the greatest number of ova in the stool suggests that reinfestation is necessary to raise the number of worms to a stage where the ova may be picked up repeatedly on stool examination. If it is not presumptuous to assume that the single discovery of ova in Cases 4 and 5 was not an error, then it seems reasonable that the patients had only a minor infestation with the parasite, one only occasionally underlined by passage of eggs. Clearly, this is speculation, however.

The prisoner of the Japanese from 1942 to 1945, who still passes *Trichostrongylus* ova at least seven years later, confirms the great potential longevity of this worm. That this patient's acquired hemolytic anemia was the result of *Trichostrongylus* infestation does not appear likely. Case 2 had both hookworm infestation and *Trichostrongylus* disease and received therapy in the form of Hexylresorcinol. The accompanying illustration displays the distorted appearance of a hookworm egg battered by two courses of therapy. In contrast, the Trichostrongylus egg has patently resisted the vermifuge, to retain its presumed pristine appearance.

The ineradicability of the disease is well known (1, 7). In the present series, adequate therapy was given to no case. For practical purposes, the only real importance of *Trichostrongylus* is the appearance of its ova. Mistaken for hookworm eggs and treated by the usual vermifuges, the persistent ova will demand increasingly frantic therapy—without results. If one is aware of the difference between hookworm and pseudo-hookworm, the patient is spared unnecessary treatment. The long duration of this infestation suggests that this problem will be present for some years after the return of American soldiers to the continental United States.

SUMMARY

If one is aware of *Trichostrongylus Orientalis*, the "pseudo-hookworm," which differs from the usual "hookworm" in that there is absence of hooks in the mouth, but which has ova almost exactly similar to those of hookworm, one will not treat fruitlessly patients with *Trichostrongylus* infestation.

CASE SUMMARIES

Case No. 1.

This 43-year-old Georgia-born Sgt. was a prisoner of the Japanese in the Philippines and in Japan from 1942 to 1945 during which time his weight decreased from 178 pounds to 80 pounds. He suffered a host of tropical diseases, but at the time of admission to Madigan Army Hospital because of jaundice noted on routine physical examination, his sole complaint was that his bowel habits had changed: prior to his confinement he had had one bowel movement daily, but since that time he had had two soft stools each day. He was a thin, jaundiced middle-aged man, but possessed an acquired hemolytic anemia which it is not the purpose of this report to discuss. Persistent in his stool were the ova of *Trichostrongylus orientalis* as well as of *Trichuris trichiura*. Proctoscopy with biopsy of the mucosa was within normal limits. The patient received three courses of Hexylresorcinol crystoids, 1 Gram each, without benefit and at the time of discharge still passed the ova in his stool.

Case No. 2.

This 20-year-old Korean war-bride, who had lived in Seoul most of her life, had been treated in Korea for *Ascariasis* in September 1951 with Hexylresorcinol. The immediate cause of her hospitalization at Madigan Army Hospital was an appendiceal abscess which was drained, cultured and studied for parasitic infestation. None was found, but stool specimens persistently showed hookworm, *Trichuris trichiura* and *Trichostrongylus orientalis*. White count was 6,200 with a 15% eosinophilia. Ultimately the patient underwent an appendectomy with the removal of a draining sinus. During her hospitalization she received 1 Gram of Hexylresorcinol on two occasions without change in the stool findings.

Case No. 3.

This 23-year-old Japanese war-bride, four months pregnant, was admitted to Madigan Army Hospital because of tuberculosis. On several occasions she was found to have *Trichostrongylus* ova in the stool. Her white count was 13,650 with a 15% eosinophilia. The patient received no therapy for parasites while in the hospital, and was discharged to a tuberculosis sanatorium.

Case No. 4.

This 31-year-old Sgt., born in Washington state, who was in Korea from September, 1950 to October, 1951, was admitted to Madigan Army Hospital because of stomatitis. White count on admission was 10,900 with 17% eosinophiles. During the patient's hospital stay his eosinophilia increased to 50% but fell to normal following treatment. Stool examination revealed *Trichuris trichiura* and *Trichostrongylus Orientalis*. Proctoscopic examination with biopsy was normal. The patient was treated with Hexylresoreinol, thereafter his stools becoming negative for *Trichuris trichiura*. The *Trichostrongylus* ova was found on only one occasion in the stool, prior to therapy.

Case No. 5.

This 33-year-old Sgt., who had been in Korea from 1950 to 1951, entered the hospital because of generalized fatigue and mid-epigastric distress. Physical examination was quite unremarkable. The white count was 7,500 with no significant eosinophiles. The stool on one occasion contained ova of *Trichostrongylus*. Proctoscopic examination was unremarkable. The patient quickly became asymptomatic.

REFERENCES

1. Craig, C. F. and Faust, E. C.: Clinical Parasitology (Ed. 5), Philadelphia. Lea and Febiger, 1951.
2. Chandler, Asa C.: Introduction to Parasitology, 8th Edition, New York. Wiley, 1949.
3. Evander, Leonard C. and Doyle, William M.: Trichostrongylus Infection in Human Beings: Need for Differentiation from Hookworm. J. Lab. and Clin. Med. *33*: 869-874, July 1948.
4. Harrison, T. L.: Principles of Internal Medicine. Blakiston Co., Philadelphia, Pa., 1950. Page 1124.
5. Lie, K. D.: Trichostrongylus Infection in Man and Domestic Animals in Java. J. Parasit *33*:359-362, August 1947.
6. Maplestone, P. A.: Trichostrongylus Infection in Man. Indian Med. Gaz. *76*:710, 1941. (Quoted by Tsuchiya).
7. O'Neal, R. and Magath, T. B.: Trichostrongylus Infection in Human Beings: Report of Three Cases. Proc. of the Staff Meetings of the Mayo Clinic, Rochester, Minnesota, May 14, 1947. *22*:193-197, 1947.
8. Sandground, J. H.: On the Potential Longevity of Various Helminths with a record for a species of Trichostrongylus in Man. J. Parasit *22*:464, 1936.
9. Schenken, J. R. and Moss, E. C.: Trichostrongylus Colubriform's in Human Appendix, Report of Case in Louisiana. J. Lab. and Clin. Med. *24*:15-17, October, 1938.
10. Shattuck, George Cheever: Diseases of the Tropics. Appleton-Century-Crofts, Inc., New York, 1951.
11. Stewart, Ian S.: Human Infestation with Trichostrongylus in South Persia. Brit. Med. J. *2*:737-738, October 1, 1949.
12. Tsuchiya, H. and Reller, Helen: A Case of Trichostrongylus Infection with Notes on the Identification of Ova. J. Lab. and Clinical Med. *30*:262-266, March, 1945.

ABSTRACTS ON NUTRITION

MASON, K. E. AND DJU, M. Y.: *Newer knowledge of the metabolism of tocopherols in human tissues.* Nutr. Symposium Series. Current Research on Vitamins in Trophology, July 1953, Nat'l Vitamin Foundation, Inc., New York.

The tocopherols, predominantly alpha tocopherol, are widely distributed in human tissues from early fetal life to advanced old age. During early postnatal life, tissue levels tend to increase slowly unless suppressed by diseases of various types. During adolescence they reach levels comparable to those of adults which, for muscle, heart, liver and certain other viscera are approximately twice those at birth, and for adipose tissue are considerably higher than in other tissues except the adrenal. In advanced age there is a tendency for tocopherols to decrease in liver and adipose tissue. Tocopherol levels, expressed as milligrams per gram of extractable fat, are maintained within a rather limited range in most tissues at all ages, but are relatively low in adipose tissue, and particularly high in the pituitary, testis and adrenal. In progressive muscular dystrophy, tocopherol levels are relatively high in the skeletal muscles and within normal range in other tissues and organs.

NICCUM, W. L., JACKSON, R. L. AND STEARNS, G: *Use of ferric and ferrous iron in the prevention of hypochromic anemia in infants.* Am. J. Dis. Child., 86, 5, Nov. 1953, 553-567.

115 full term infants were given ferric iron as ferric ammonium citrate and 37 full term infants were given ferrous iron as ferrous sulfate. Only 5 mg. of iron were given daily to infants 3 to 6 months of age and 10 mg. daily to older infants. Such doses prevented the onset of hypochromic anemia. The iron was mixed with the formula. It was found, however, that ferrous iron in the same dosage permitted significantly higher hemoglobin values in infants than did ferric iron.

PATON, J. B. *and* WELLBY, M. L.: *Analysis of amino acids present in biological material by chromatographic methods suitable for routine clinical use.* Med. J. Australia, Oct. 24, 1953, 639-644.

Paper chromatography was used in detecting the amounts of certain amino acids in blood serum, urine, and other bodily fluids under various conditions. One thing stands out prominently—a tendency to constancy of amino-acid concentrations of serum under all conditions. Even following the intravenous injection of hydrolyzed casein, elevations of amino-acid concentrations were rather evanescent. Even after a protein meal, the serum and the urine showed remarkably little deviation from fasting normal. In the ninth month of pregnancy there is some increased concentration of amino acids in serum and urine. Even in severe liver damage, the pattern usually is not much disturbed.

MENEELY, G. R., TUCKER, R. G., DARBY, W. J. AND AUERBACH, S. H.: *Chronic sodium chloride toxicity: hypertension, renal and vacular lesions.* Ann. Int. Med., 39, 5, Nov. 1953, 991-998.

The authors suspected that excess consumption of sodium chloride might be a factor in degenerative disease. A long term study was undertaken in male albino

rats. Purified rations, containing from 0.01 percent to 9.8 percent of NaCl and water were fed at will from the age of 5 weeks. Diets both high and low in NaCl reduced the rate of growth. A low-sodium diet depressed the appetite, but diets high in NaCl did not. Edema developed in 18 percent of the rats eating diets which contained from 7.0 percent to 9.8 percent NaCl. Pathological lesions are observed in the kidneys and to a lesser extent in various other tissues of rats consuming high levels of salt. Sustained arterial hypertension was observed in the rats eating high levels of NaCl after 9 months of the dietary regime.

FREEMAN, J. T.: *Clinical correlations in geriatric nutrition.* J. Clin. Nutrition, 1, 6, Sept.-Oct. 446-452.

Lipase production is lower in old age, and this is an absolute functional loss without obvious compensation. Other things being equal, fat in the diet should be reduced to about 1 gram, or 9 calories, per kilogram per day. Usually carbohydrates should constitute one-half of the total daily caloric intake—i.e. 3 grams, or 12 calories per kilogram per day. The protein fraction of the diet should constitute at least 20 percent of the daily food intake—about 1.35 grams per kilogram per day, or just over 5 calories per kilogram.

Old people are like young people with certain exceptions. Appetite usually decreases. Activity almost always is reduced. Serious gastro-intestinal lesions may be almost symptomless. The incidence of gastric ulcer is very high in the 65 to 74 year group (33.4 per 100,000). Cancer of the digestive organs becomes even more pronounced. Nutrition, although an important part of the gerontologic approach, cannot be used as a substitute for all its therapeutic procedures. The non-nutritional components of clinical management are inextricably involved with dietary considerations and form an essential aspect of the treatment of the elderly patient.

GOWEN, G. H.: *Screening for diabetes.* Ill. Med. J., 104, 5, Nov. 1953, 293-94.

Gowen describes the urine testing program conducted at the 1953 Illinois State Fair, at Springfield, Illinois. Out of 1657 specimens from presumably normal persons, there were 247 positive for glucose. Very little resistance was encountered in persuading individuals to submit samples.

GHOSH, J. C.: *Planning for food and population.* Calcutta Med. J., 50, 8, Aug. 1953, 287-298.

Ghosh presents an excellent review of the industrial, agricultural and nutritional conditions in current India. The essential problem is to provide work and food for a population which, year after year, has gotten out of hand. He makes many suggestions with respect to improving food supplies, but always he is faced by the fact that in the rural areas, 285 million people are doing the same work which could be accomplished by 50 million. He tries to siphon off this excess population into industries, but industry cannot expand to accommodate them, because of a lack of risk capital. He comes to the obvious conclusion that perhaps the greatest single benefit is to be obtained by teaching the people in the rural areas the reasons for and the technique of birth control, and providing them with the physical means of contraception.

WADSWORTH, G. R. AND OLIVEIRO, C. J.: *Plasma protein concentration of normal adults living in Singapore.* Brit. Med. J., Nov. 21, 1953, 1138-39.

The plasma protein concentration of 80 men and 59 women was measured by the copper sulfate specific gravity method and found to be 7.8 gms. and 7.6 gms. per 100 ml. respectively. (The accuracy of the method was tested against estimations of total nitrogen by the macro-kjeldahl method, and close agreement found). The difference between the mean plasma protein concentration of Asians and of Europeans was not statistically significant. The findings suggest that living in a warm climate might be associated with a relatively high plasma protein concentration which is not a result of dehydration or of increased antibody formation.

GOODMAN, J. I.: *Hepatomegaly and diabetes mellitus.* Ann. Int. Med., 39, 5, Nov. 1953, 1077.

Goodman sought to determine clinically a possible relationship between enlargement of the liver and the state of diabetic control. He percussed the liver in 459 diabetic patients. The liver was enlarged in only 9 percent of patients with controlled diabetes; in 69 percent of those with uncontrolled diabetes and in 100 percent of patients with keto-acidosis. He feels that polyuria, polydipsia, the presence of neuropathy or hepatomegaly are better indications of the state of the patient than the total amount of glucose excreted in 24 hours. The occurrence of a greatly enlarged, frequently tender liver in every patient with keto-acidosis points to this organ as being a major factor in producing the abdominal manifestations of this condition.

OAKLEY, W.: *"Lente" insulin (insulin zinc suspension): further studies.* MURRAY, I. AND WILSON, R. B.: *The new insulins—lente, ultralente and semilente.* NABARRO, J. D. N. AND STOWERS, J. M.: *The insulin zinc suspensions.* GARITZEN, F.: *The classification of various insulins.* British Med. J., Nov. 7, 1953, 1021-1031.

Hallas-Moller and associates at the Novo Laboratories in Copenhagen have produced three new insulins, called Lente, Ultralente and Semilente. The corresponding British names are Insulin zinc suspension, Insulin zinc suspension (crystalline) and Insulin zinc suspension (amorphous). Hypoglycemic effects are maintained by the first of these for about 24 hours, by the second for 30 or more hours and by the last for 12 to 16 hours. The lente form is not satisfactory in many patients who require more than 48 units per day. However, nocturnal reactions were uncommon and hypoglycemia rarely occurs in the early hours of the morning. The introduction of these insulins has created considerable confusion. It should be remembered that regular insulin acts for about 8 hours. For 10 hours' duration, one may use NPH, semilente (Novo) and zinc insulin "neutrale" (Organon). For 16 hours' duration, one may use globin insulin and lente (Novo). For 18 hours' duration, protamine zinc insulin and ultralente (Novo) are the ones with longest action. It is quite obvious that physicians must become ac-

quainted with the actions of the many insulins available only by personal use and study on their patients.

BAYNE, G. AND BOGER, W. P.: *Vitamin B_{12} supplementation of the diets of healthy adults: a study of weight changes employing a Latin square design.* J. Clin. Nutrition, 1, 6, Sept.-Oct. 1953, 424-429.

Two schedules of oral vitamin B_{12} supplementation, namely 100 mcgm. daily for 3 months and 30 mcgm. three times daily for 3 months were evaluated in conjunction with a placebo given daily for 3 months. There was no significant weight gain attributable to vitamin B_{12} administered in this group of 44 healthy adult females given an *ad libitum* diet for the 12 month period encompassed by the control and treatment phases of the study.

WILSON, H. T. AND SINK, F. H.: *Hypopotassemia in human starvation and gastric resection.* J Clin. Nutrition, 1, 6, Sept.-Oct. 1953, 430-435.

Three cases of long-standing starvation and resultant potassium deficiency are described. Potassium deficiency may be a frequent feature of starvation. Flat T waves with prolongation of the QT intervals in the EKG, and certain nervous symptoms such as a-reflexia, muscular weakness, mental retardation, dysarthria, emotional lability and disorientation are often present. Improvement by giving potassium requires time.

EDITORIAL

THE FOOD AND POPULATION PROBLEM IN INDIA

India still presents one of the most acute, yet chronic, examples of a population constantly outgrowing its food supply. Wide-spread malnutrition, particularly in the rural areas, is perennial. Actual famine is not uncommon. Britain failed to solve this basic problem in India because of the inherent difficulties it presented, and, since Independence, the leaders of India are facing precisely the same puzzle. It is a problem intricately tied in with the whole labor, industrial and educational status. Essentially, the situation is that there are 285 million rural inhabitants who are doing the work which could be accomplished by only 50 million, provided modern farming technology could be introduced and paid for. It would be possible to siphon off the excess rural population into industry except for the fact that industry cannot be sufficiently expanded to accommodate these millions. India cannot save the money to promote such an expansion and there is a natural indisposition to accept foreign capital, even if it were offered, because of the many political strings which would be attached to it.

Disease, especially malaria, is a scourge which still requires to be brought under control. There is an increase of no less than 50 million population every ten years. The devastation of malnutrition and disease is so great that 50 percent of the rural population die before they have become bread-winners. It is utterly impossible to produce satisfactory diets for almost *any* social class in India, and the rural inhabitants subsist on 2,000 calories or less with a noticeable absence of protein of high biological value.

Too many people—too little food! Why not encourage emigration of the rural inhabitants to other, empty lands? This is impossible because the people of India will not emigrate, in fact they will not even emigrate from one section of India to another.

Nehru, himself, was chairman of the National Planning Committee, established in 1938 by the Indian National Congress for the purpose of studying the entire, complicated situation. After a number of years, the report of this committee received general acceptance by the Congress. The chief recommendation was the necessity of "family planning"—in other words, birth control. It was suggested that cheap and safe methods of control be adopted and birth-control clinics established. It was hoped, after Independence, that something would be done about the committee's recommendations. Ghosh (1) has recently stated that he is disappointed. The final *impasse* was the political inexpediency of an unpopular crusade.

The writer of this Editorial is not necessarily taking a position either favorable or unfavorable to the adoption of birth control under these or any other circumstances. It is ironical, however, that the Committee, in horror at the continued spectacle of malnutrition, starvation and death was forced to make such radical recommendations, only to see these recommendations disregarded by Congress. It would seem that if birth control is to be instituted, it must come via the slow process of secular education.

(1) Ghosh, J. C.: Planning for food and population Calcutta Med. J., 50, 8, August 1953, 287-298.

BOOK REVIEWS

DAS INSELSYSTEM DES PANKREAS. H. Ferner, Stuttgart, Georg Thieme, 1952.

This book is concerned mainly with morphology of the islets of Langerhans with emphasis laid on the two types of islet cells, namely, the beta cells which are well known as the site of insulin production, and the alpha cells whose endocrine activity remains unclear. The author gives in detail the modern staining tech-

nics which permit the differentiation of islet cells, including his own modification of the Gros-Schultze silver stain particularly suitable for the identification of alpha cells. Considerable and very valuable information is contained in the chapter on the development of the insular apparatus in man, from fetal to adult life. The chapter devoted to islet histology in the adult provides interesting data on the blood and nerve supply of islets. Comparative nesocytology is dealt with in detail and covers the quantitative, cytological and topographic relationships of islets in various species, including the horse and the bat. The author points out that because of marked species differences specific staining methods are needed for each species.

The central theme of the book is Ferner's theory that diabetes is due not to insulin insufficiency but to an increase in alpha and decrease in beta cells, with the resulting increase in the A:B ratio. It has been known for years that pancreatic extracts contain a substance apt to cause a transient rise of the blood sugar content (the so-called glucagon or hyperglycemic-glycogenolytic factor), but while most workers in the field assigned its elaboration to alpha cells, recent work revealed that selective destruction of these cells is followed by a rise and not a drop of blood glucose. Thus the primary importance of alpha cells in the etiology of diabetes remains undemonstrated.

To strengthen his thesis, the author makes a number of statements which are open to criticism. He explains, for instance, the hypoglycemia of the dumping syndrome as due to loss of alpha cells in the resected stomach and gut. The fact, however, is that such patients do not suffer from continuous hypoglycemia, and in glucose loading tests show an initial marked rise in the blood sugar content. It is known that the newborn and the growing child have a higher proportion of alpha cells than the adult, without a concomitant hyperglycemia, and show rather a tendency to low blood glucose values. Ferner's contention that this phenomenon results from increased peripheral utilization of sugar in the growing child is not supported by experimental evidence. The fact that diabetes does not develop after partial pancreatectomy he explains by the normal A:B ratio in the remaining portion of the gland, while the diabetes after total pancreatectomy he attributes to activity of alpha cells in the gastro-intestinal tract. The inconsistency of this concept is obvious. As for diabetes, one must of course take exception to the author's complete disregard for the extrapancreatic factors involved in the carbohydrate metabolism at the tissue level.

The great value of this book lies not in the author's dual concept of islet function, but in the factual material he has presented as well as in beautiful illustrations he has chosen with care. While his theory cannot be validly applied without more knowledge on the function of the alpha cells, the concept of the A:B ratio represents an important contribution to morphologic studies of islets in relation to disorders of the carbohydrate metabolism.

In a book written by an author of Ferner's caliber the numerous orthographic errors are most surprising. To quote but a few, on page 171 Borchardt's name appears as Borchard, and Minkowski's name is misspelled on page 134. Surprising, too, is the incompleteness of bibliographical data. Thus, for instance, on page 77 the author quotes the work of Bouckaert and De Duve and on page 75 that of Kimball and Murlin, but fails to list them in his bibliography. Disregarding these shortcomings the book may be highly recommended to students of pancreatic pathology in relation to disorders of the carbohydrate metabolism.

Maximilian Fabrykant, M.D.

THE ENGLISH COMPLAINT. Franklin Bicknell, D.M., M.R.C.P. William Heineman, Ltd., Toronto. Canada.

Bicknell is a physician in England, vice-chairman of the Food Education Society, a member of the Nutrition Society and English Editor of *International Zeitsrift Vitamin forschung*. For several years he has been kicking up quite a rumpus in England. His book "Dying England" (1947) explained how the poverty of the diet was stultifying Englishmen. This book caused heated debates both in the House of Lords and The Commons. The public naturally backed up the author.

The main thesis of this present book is that the universal fatigue complained of by all persons in England is traceable to insufficient food and food of poor quality. Bicknell is more or less an enemy of all prepared foods. Many of his contentions with respect to the harmfulness of stale or prepared foods naturally are debatable. No doubt his chief points are well taken. The book is worth reading because of its informal style which "pulls no punches."

GENERAL ABSTRACTS OF CURRENT LITERATURE

HEILIG, R. AND SHARMA, R. K.: *Aureomycin and terramycin in infective hepatitis and hepatic coma.* J. Indian Med. Assn., XXII, 12, Sept 1953, 481-485.

One case of hepatitis without coma, and one with beginning coma responded to aureomycin orally although the first case had proved refractory to all other forms of treatment for more than two months. Two other cases, already in deep coma, responded favorably to routine therapy, plus the use of intravenous terramycin. Thus, 3 of the 4 cases probably would not have survived without the use of aureomycin or terramycin. Both these preparations appear to possess antiviral activity.

ALEXANDER, F. K.: *The prepyloric suspect lesion.* Radiology, 61, 4, Oct. 1953, 523-533.

A profusely illustrated article showing x-ray findings along with clinical histories in a number of patients. The impression gained is that, no matter how small or large a prepyloric defect may appear, it may

turn out to be a cancer, a peptic ulcer, or even merely adhesions. Certainly when such lesions are detected, early operation should be undertaken because, in many cases resembling ulcer, we are dealing with a cancer.

GARVEN, A.: *The diagnosis and treatment of epidemic diarrhea.* Med. J. Australia, Sept, 19, 1953, 447-450.

Gastro-enteritis in a children's hospital is still a largely unsolved problem because, in one half the cases, the etiology is completely mysterious. In a small percentage of cases, two groups may be isolated which are pathogenic beyond any question. These are the Salmonella and the Shigella groups, the former consisting of some hundreds of types, and the latter with its two main types, S. sonnei and S. flexneri. Salmonella affects chiefly babies under 2 years of age while the Shigella organisms chiefly affect toddlers over two and the pre-school child. There are about six strains of B. coli which are pathogenic and were formerly referred to as D.433, but are now named in terms of the O, B and H antigens. Of the Paracolon Bacilli, two groups only are considered causative of gastro-enteritis. Except in two instances, all attempts to isolate a virus from the stools of patients with gastro-enteritis have been unsuccessful.

FRIEDMAN, A. P.: *Recent concepts in migraine and tension headaches.* Am. Pract. and Dig. Treat., 4, 11, Nov. 1953, 762-764.

For the treatment of a migraine attack the most effective method is the rectal suppository of ergotamine tartrate and caffeine. For tension headache the immediate treatment of greatest value is a combination of sedatives and analgesics. Diagnostic differentiation between the two types is usually not too difficult merely from the history. Tension headaches do not have preheadache symptoms whereas migraine almost always has prodromata of visual disturbance, gastro-intestinal upset or psychological upset. In both kinds of headache a study of the personality is essential and psychotherapy is effective, especially via ventilation, environmental manipulation and re-education. Both headaches represent the end results of undue stress upon the organism, and probably hormonal influences are operative.

AL-HAMAMI, A.: *Aureomycin in the treatment of amebiasis: preliminary report.* Jour. Med. Professions Assn., Baghdad, 1, 1, March and June 1953, 3-7.

The author used aureomycin in seven cases of amebiasis. Five cases were chronic, one was acute and one had a liver abscess. He found the results very encouraging. The only toxic symptoms observed were nausea and vomiting.

FAIK, S. AND ADIB, R. S.: *Adenocarcinoma of the lower end of the esophagus.* Jour. Med. Professions Assn., Baghdad, 1, 1, March and June 1953, 42-54.

A case of carcinoma of the lower end of the esophagus is presented, with successful resection via a purely transthoracic approach and esophagogastrostomy. Certain ideas about operative technique are discussed.

BROWN, P. W.: *Regional enteritis.* Am. Pract. and Dig. Treat., 4, 11, Nov. 1953, 774-776.

Regional enteritis is a nonspecific granulomatous disease of the small intestine; characterized by necrotizing, ulcerating, inflammatory changes in the acute phase, and cicatrizing, inflammatory changes in the chronic phase, with a tendency to the production of internal and external fistulas. Diagnosis is made on the basis of the x-ray findings. The cause is unknown. In 90 percent of cases the disease involves the ileum. Medical treatment is merely symptomatic and supportive—blood transfusions, vitamins and sedatives, with high protein diet. In some cases resection of the involved portion of gut has resulted in cure, but, in general, the end of results of surgery, as of x-ray therapy, are not encouraging.

MORRIS, J. B.: *Transpyloric prolapse of redundant prepyloric gastric mucosa.* Northwest Medicine, 52, 10, Oct. 1953, 836-838.

Prolapse of gastric mucosa into the duodenum has been proven to be a pathological entity and one of probable clinical significance in a small but undetermined percent of cases. Owing to marked variation in incidence as reported by x-ray examination, infrequency of surgical and pathological check on the diagnosis, and the frequent association of other organic and functional conditions which might explain the symptoms, we have a serious lack of knowledge regarding the clinical significance of the condition.

At present a conservative attitude should be adopted and radical surgery avoided until more is known about the condition.

SWYNNERTON, B. F. AND TANNER, N. C.: *Chronic gastric ulcer: a comparison between a gastroscopically controlled series treated medically and a series treated surgically.* Brit. Med. J., Oct. 17, 1953, 841-847.

A review and follow-up of 498 patients with chronic gastric ulcer, about one-half of whom were treated medically and one-half surgically, seems to indicate that surgery offers the best results provided expert surgical skill is available and provided the patient does not have too much else wrong with him. Pyloric ulcers are exceptional in women. The age of the patient does not appreciably affect the degree of gastric acidity. One-quarter of the patients in each series have died in roughly ten years, there being no predominant cause of death. Any association of gastric cancer with gastric ulcer is considered to be due to the presence of a "degenerate mucosa."

BARTA, F. R.: *Psychosomatic medicine—a new approach.* Nebraska State M. J., Sept. 1953, 38, 9, 320.

Barta, Director of the Department of Neuropsychiatry at Creighton University School of Medicine, has made an original division of people in 4 groups on the basis of how well satisfied they are with themselves and also how much they prefer the advice of others. Arranging some 148 cases of physical diseases according to their incidence among the various types of "temperament," he finds, for example, that peptic ulcer is by far commonest among people who, while being

taught to abide by their own judgment are unconsciously dissatisfied with their own ability. Rheumatoid arthritis was by far most common among those who were taught to abide by the judgment of others but are satisfied with their own ability. It is suggested that this study opens up a new angle of approach to the psychosomatic investigation of disease.

DUTTON, W. A. W. AND BLAND, H. J.: *Hiatus hernia and pregnancy.* Brit. Med. J., Oct. 17, 1953, 864-866.

Nine cases are reviewed in which hiatus hernia was diagnosed during pregnancy. The usual symptoms were substernal distress while lying down, nausea, prolonged vomiting and, in some cases, serious hematemesis requiring blood transfusions. Almost always the symptoms disappeared following labor, due to relief of intra-abdominal pressure. In those who became fat later on, the symptoms returned, and in some, surgical cure of the hernia was required. One problem that arises is with respect to how frequently an undiagnosed hiatus hernia may contribute to the usual gastric symptoms of pregnant women. A larger series is needed before this question can be answered.

KRAUS, H.: *Chronic diarrhea: a clinical and laboratory study of 39 cases.* U. S. Armed Forces Med. J., IV, 11, Nov. 1953, 1584-1586.

Thirty-nine patients with a history of chronic diarrhea were studied by extensive parasitological and bacteriological techniques to determine the various causative agents involved. *E. histolytica* was found in 69 percent. No bacterial pathogens were isolated. One patient had sigmoidoscopic and x-ray evidence of chronic ulcerative colitis. It is to be noted that these cases were U. N. soldiers seen at the Tokyo Army Hospital in Japan.

KEANEY, E. P., STUBENBORD, J. G., MCLEAN, M. M. AND BOVE, F. A.: *A hypertension and diabetes detection program.* U. S. Armed Forces Med. J., IV, 11, Nov. 1953, 1613-1620.

The detection program was directed toward the civilian workers in the U. S. Naval Shipyard at Philadelphia, Pa. For some time routine chest x-rays had been made. Some 5,250 workers, however, were given blood-pressure readings and urinalysis, a procedure requiring only 15 minutes. The upper limits of normal for blood pressure were taken to be 140 systolic and 90 diastolic. Using these criteria, hypertension was detected in 12 percent and diabetes mellitus was detected in 3 percent. The older age groups (over 40) were examined.

MACALPINE, I.: *Pruritus ani. A psychiatric study.* Psychosomatic Med., XV, 5, Sept.-Oct. 1953, 499-508.

Macalpine found from a careful psychological study of 64 cases of pruritus ani, that the condition could be resolved by psychotherapy. Pruritus ani always is associated with bizarre gastrointestinal symptoms and sexual disorders. Its origin can be traced to a reactivation in adult life of infantile (unconscious) fantasies about procreation centering around the anal function. These "cloacal" fantasies are revived in their original primitive mode, as bodily sensations rather than ideas, so that the symptoms represent the fantasy. Once the patient has been led cautiously to a self-realization of the existence of the fantasy, relief results.

HELLER, M. H., LEVINE, J. AND SOHLER, T. P.: *Gastric acidity and normally produced anxiety.* Psychosomatic Med., XV, 5, Sept.-Oct. 1953, 509-512.

Two hospitalized patients were given two routine gastric acid intubations on two successive days. On the second day, some anxiety over the need for the second intubation was manifest by each patient. Fractional samples of free and total acids for the two days showed that in each case acid levels were significantly higher on the second day. These elevations were attributed to the anxiety normally induced by the situation. The presence or absence of upper G. I. symptoms made no difference in the results.

BAKER, A. B. AND LUDEN, T. E.: *Carcinoid of the rectum.* Northwest Med., 52, 11, Nov. 1953, 930-931.

Carcinoid of the rectum is a rare disease, only 72 cases having been reported to date. Seven of these cases have reportedly been malignant in their clinical behavior. In the case reported by the author, the lesion was small and was treated by simple excision, with good results in a 3 year follow-up. Ultimate decision as to the best therapy must await careful case follow-ups.

STECK, L. G.: *Mesenteric hernia complicating pregnancy.* Northwest Med., 52, 11, Nov. 1953, 931.

Steck describes a case of pregnancy near term in whom a toxic, febrile condition suddenly developed with almost immediate cessation of fetal heart sounds. Laparotomy revealed herniation of 200 cm. of small bowel through a thumb-sized hole in the mesentery. Gangrenous bowel was resected and the patient recovered. Her toxic condition was thought to be responsible for fetal death.

LIDDELOW, B.: *Serum protein levels in normal non-pregnant and pregnant women.* Med. J. Australia, 40, 9, Aug. 29, 1953, 332-334.

The maximum, minimum and average serum protein values are reported for 23 normal non-pregnant women and for 20 women in each month of pregnancy. There is a slow decline in serum protein concentration until the last month, when a slight rise occurs.

CASS, L. J. AND FREDERIK, W. S.: *Malt soup extract as a bowel content modifier in geriatric constipation.* Journal Lancet, Oct. 1953, 414-416.

A malt soup extract (Borcherdt Malt Extract Co., Chicago) consisting of a watersoluble mixture of sugars and grain extractives processed from barley malt was used on 24 badly constipated persons, using from 2 to 4 tablespoons per day. In all cases soft stools were produced without any ill effects, so that in almost all cases laxatives or enemas did not need to be used, although the malt soup extract cannot be regarded as a laxative.

HAMILTON, D. G.: *Diarrhea and vomiting in children.* Med. J. Australia, Sept. 19, 1953, 450-452.

The successful treatment of gastro-enteritis depends on the proper replacement of fluids and electrolytes at first by intravenous injection if necessary and then by mouth, followed by the uses of a carefully graded diet. All other considerations are of minor importance. Water, sodium, potassium, protein and calories are the elements to be properly replaced. Occasionally morphine may be cautiously used.

FINCKH, E. S., BAKER, S. J. AND RYAN, M. M. P.: *Value of liver biopsy in the diagnosis of tuberculosis and sarcoidosis.* Med. J. Australia, Sept. 5, 1953, 369-374.

Liver biopsy was done on 7 patients suffering from pyrexia of unknown origin and on 9 patients with obscure chest lesions. In 8 of these patients granulomata resembling tuberculosis or sarcoidosis were found. In one case, inoculation of biopsy material into guinea pigs produced a positive finding of M. tuberculosis. Liver biopsy also was done on 25 patients with proven tuberculosis but in only 2 were granulomata found. Such liver biopsies are of value in the investigation of patients with fever of unknown origin.

DR. ARIAS VALLEJO: *Sociodietetic prophylaxis of diabetes. Rev. Espanolade* Las. Enf. Del. Ap. Dig. De La Nutr. Vol. 12, No. 6, 559-570, Nov.-Dec., 1953.

The development of diabetes mellitus in the course of the patient's life may be facilitated, or rather accelerated by certain exogenous factors. One of these, perhaps the most important, is food. A normal diet kept by a subject predisposed to diabetes may sooner or later progressively decrease the endocrine functioning of his pancreas, thus favoring the development of the diabetic syndrome by abnormally increasing the langerhansian hormone requirements. This is where the opportunity for efficient prophylaxis of diabetes becomes apparent.

It is therefore only natural to reduce the patient's insulin requirements, to prevent obesity before it appears and to induce weight loss when it is already present. A prophylactic diet should contain the necessary amount of calories; its protein content should be high, and its carbohydrate and fat contents low. The main aim of this dietary prophylaxis should be the maintenance of the ideal weight of each patient.

Dietary prophylaxis of diabetes cannot be applied to the general population but only to those people predisposed to the condition. In the selection of people thought likely to develop diabetes the children of diabetics should be considered with special care, since the importance of inherited tendencies is generally accepted. It is likewise necessary to pay attention to obese patients, women during pregnancy and subjects who suffered from infections due to pancreatotropic viruses as well as to subjects indulging in a high-sugar diet.

The general practitioner is the main agent in the prophylaxis of diabetes. Private or Government institutions concerned with the prevention of diabetes should make intensive propaganda by means of books, scientific articles, direct or broadcast lectures or simply by means of posters. This propaganda should be primarily directed to the general practitioner, then to the offspring of diabetic patients and finally to the rest of the population.

SOMAN, D. W. AND MODI, B. G.: *Enteric fever in Bombay—ten years' review of laboratory diagnosis.* J. Indian Med. Assn., XXIII, 2, Nov. 1953, 47-52.

The Haffkine Institute, Bombay, India, during the past 10 years, has examined 15,235 samples of blood, both by culture and Widal tests. Out of these, 6,042 (40 percent) were diagnosed as enteric fever by both tests, 3,885 (14 percent) by Widal alone, and 2,157 (14 percent) by culture alone. It is noteworthy that one-third of the bacteriologically proved typhoid cases gave negative Widals, Both blood and clot cultures should be done routinely as the results of both are not always identical.

ETTER, L. E.: *Left-sided gallbladder (necessity for film of the entire abdomen in cholecystography).* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 70, 6, Dec. 1953, 987-990.

Etter describes 2 cases of left-sided gallbladder, in both of which the organ was normal. Such a left-sided organ could easily be missed if only conventional 10x12 inch films are exposed on the right side of the abdomen during cholecystography. In such cases an erroneous report of non-functioning, presumably diseased gallbladder may be made even after a double dose of contrast medium on repeat examination. To avoid this error, it is suggested that a 14 by 17 inch film of the abdomen be used in cholecystography when the gallbladder is not visualized on a 10 by 12 inch film.

WAIT, L. P.: *Congenital hypertrophic pyloric stenosis in identical twins.* Med. J. Australia, Oct. 31, 1953.

Wait found easily-diagnosed congenital hypertrophic pyloris stenosis in each of identical twins at the age of 12 weeks. After resuscitation with blood transfusions and glucose, Ramstedt's operation was performed on each of them, and they are both getting along well, two years later.

25TH ANNUAL MEETING OF THE AERO MEDICAL ASSOCIATION

The Aero Medical Association announces its forthcoming 25th Annual Meeting to be held at the Hotel Statler, Washington, D. C., March 29-31, 1954.

This being the Silver Anniversary of the Association (founded in Detroit, Michigan in 1929), an outstanding scientific program and calendar of social events is being arranged under the direction of the President of the Association, Rear Admiral Bertram Groesbeck, Jr., Medical Corps, USN, retired, Director, Department of Health, State of Indiana.

NEWS RELEASE

E. Machlett & Sons has just announced the publication of an attractively illustrated folder entitled "Avoid Costly Breakage with Machlett Polyethylene Laboratory Ware." Included in the folder are 11 "everyday" laboratory items of all sizes ranging from polyethylene policemen to 13 gallon polyethylene carboys. Though these products are clearly illustrated, detailed descriptions — including dimensions — are also given. Both unit and quantity prices are listed for all items and all sizes. Copies of this folder are available from E. Machlett & Son on request.

R.P.I. ELECTS SCIENTIST TO BOARD OF DIRECTORS

Troy, N. Y.—Election of Dr. Maurice L. Tainter, vice president of Sterling Drug Inc. and director of the Sterling-Winthrop Research Institute, Rensselaer, N.Y., as a trustee of Rensselaer Polytechnic has been announced by Dr. Livingston W. Houston, president of R.P.I.

Dr. Tainter is one of the leading pharmacologists in the United States. He is the author of many scientific papers and has given numerous lectures on therapeutic research and allied subjects at various medical and technical meetings in this country and abroad. Among the notable achievements credited to the Sterling-Winthrop Research Institute is the development of such important drugs as the antimalarial compounds Atabrine, Aralen and Plaquenil, the latter two being noted as a cure for malaria; Milibis, for amebiasis; Levophed, a life-saving drug to treat shock and serious heart attacks; Ravocaine, a potent local anesthetic; and Telepaque, an x-ray contrast medium regarded as invaluable in diagnosing gallbladder conditions.

Dr. Tainter is a member of the Board of Governors of Union University and a trustee of the Albany College of Pharmacy. He is also president-elect of the New York Academy of Science.

Prior to his appointment as director of the newly established Research Institute in 1946, Dr. Tainter had been professor of pharmacology at Stanford University Medical School, from which he had received his A.B., M.A. and M.D. degrees. He was also head of the Division of Physiological Sciences at the College of Physicians and Surgeons Dental School, San Francisco. He was awarded an honorary D.Sc. degree by R.P.I.

Dr. Tainter is a member of many national and international professional societies, including the American Association for the Advancement of Science, American Medical Association, American Society of Pharmacology and Experimental Therapeutics, International Association of Dental Research, and American Pharmaceutical Association. He has been elected a foreign member of the Cuban Academy of Sciences, and he is also an honorary member of the California State Dental Association, American Society of Anesthesiology, Argentine Medical Association, and others.

LEVOPHED AIDS RECOVERY FROM SHOCK IN 6 OF 7 CASES OF HEART FAILURE THROUGH CARDIAC AND PRESSOR ACTIVITY

Six of seven patients recovered from severe shock accompanying myocardial infarction, despite a diagnosis of congestive heart failure, following infusions of the pressor amine, Levophed, according to a report in *Circulation* (8:883, Dec., 1953).

In five additional patients in the same condition, immediate pressor responses were obtained with another sympathetic amine but the blood pressures failed to stabilize, report Drs. Peter C. Gazes and Leon I. Goldberg, and Thomas D. Darby of the Department of Pharmacology, Medical College of South Carolina, Charleston.

Discussing the problem of shock in myocardial infarction, the authors cite previous studies attributing the shock state to failure of the heart as a pump, peripheral vascular collapse, or a combination of both. Levophed's effectiveness in treating shock had been traced primarily to its potent vasoconstrictor action.

However, the drug also has a "powerful augmenting action on the contractile force of the heart and may thus be beneficially used in shock of either of the above types," report Dr. Gazes and his associates.

"Levophed was found to produce pronounced increments in heart contractile force, in addition to pressor effects, in unanesthetized, trained dogs."

The doctors also observed an increase of contractile force in seven patients with signs of congestive heart failure in addition to shock.

"In these patients there was an almost immediate clearing of pulmonary congestion, increase in intensity of heart tones, increase in pulse pressure and decrease of distension of arm and neck veins."

Levophed's activity in this respect, the paper points out, is "a basis for the high recovery rate observed in the treatment of shock accompanying myocardial infarction, particularly in those cases with associated congestive heart failure."

ROBINS CO. INC.

In line with their previously announced policy against substitution, the A. H. Robins Co., Inc., of Richmond, Va., has instituted legal proceedings against a number of retail druggists in Brooklyn, N. Y. The Robins Co. charges that on several occasions these druggists filled prescriptions specifying "Pabalate" with another product similar in size, shape and color not manufactured by Robins Co.

The Robins Co. has asked the court to enjoin these druggists from further substitution of their products and has petitioned the court

to determine and award suitable damages as well as court costs and attorney fees incurred as a result of such substitution.

McGILL'S 1954 CUSHING LECTURE

CHICAGO — Max Thorek, M.D., of Chicago, delivered the 1954 Cushing Memorial Lecture January 15 before the faculty of the medical school of McGill University in Toronto. Dr. Thorek, who is founder and secretary-general of the International College of Surgeons, and professor of surgery at Cook County Graduate School of Medicine, spoke on "Impending Death under Anesthesia." He reported a case of cardiac arrest during an appendectomy under spinal anesthesia and pentothal sodium in a woman of 23, who ultimately recovered without apparent permanent cerebral damage although her heart was stilled for 19 minutes. The paper emphasized the need for constant alertness and immediate action, including oxygen, cardiac massage and artificial respiration. Included also were a review of the literature, a discussion of the physiology and prophylaxis and treatment and the biochemistry of cortical damage.

SCHERING SENDS REAL GALLBLADDER X-RAYS TO RADIOLOGISTS IN UNUSUAL MAIL PIECE

Actual gallbladder x-rays taken by clinical investigators using Teridax constitute the first direct mail piece of its kind, sent to all of the country's radiologists by Schering Corporation, Bloomfield, New Jersey, pharmaceutical manufacturers.

Two typical gallbladder x-rays following use of Teridax are on the piece. Radiologists may clip them to the viewing box to see the advantages of the preparation.

Teridax, or Triiodoethionic acid, is a new radiopaque substance. It has been found to produce the desirable density in gallbladder x-rays, with no confusing opacities in the colon, according to numerous published clinical reports.

The two x-rays demonstrate the effectiveness of Teridax in a 10 to 12 hour interval, with a dose of 5 tablets. There are no side actions.

The mail piece is packaged in a sturdy cardboard folder, on which is printed "X-ray, Do Not Fold."

ESTABLISHMENT OF RUSSELL M. WILDER FELLOWSHIP

The National Vitamin Foundation invites individuals holding doctorate degrees in medicine or one of the biological sciences, who are interested in continuing their training in the science of nutrition, to become candidates for the newly established Russell M. Wilder Fellowship.

This post-doctorate fellowship was created by the Foundation to honor Dr. Russell M. Wilder, of the Emeritus Staff of the Mayo Clinic for his more than forty years of devoted service and significant contributions to medicine and public health, and particularly for his leadership in advancing our knowledge of diseases of metabolism and nutrition.

In establishing the fellowship, the Foundation expresses its feeling of deep appreciation to Dr. Wilder for his pioneering work and provides, upon his retirement, an opportunity to a qualified young scientist to equip himself for a career inspired by Dr. Wilder's example. The fellowship is one more important step taken by the Foundation in its continually growing program directed to the purpose that the health and welfare of mankind may be improved through better nutrition.

1. The Fellowship is for 3 years and pays the recipient $4,500 the first year, $5,000 the second, and $5,500 the third year. It becomes effective September 1, 1954.

2. Application forms can be obtained from the offices of The National Vitamin Foundation at 15 East 58th Street, New York 22, New York.

3. Candidates must mail their completed application forms to the Foundation on or before March 15, 1954.

4. Applications must be accompanied by a letter from the executive officer of the institution where the work is to be done and by a letter from the head of the department under which the candidate is to work, attesting to the fact that the candidate will be permitted and encouraged to carry on his work and studies in the institution and department indicated.

5. The candidate must outline a program of investigation which must be approved by his preceptor.

6. The candidate must give reasonable assurance that he will complete his fellowship and continue to work in the field of nutrition following the period covered by the fellowship.

7. The successful candidate will be chosen by The National Vitamin Foundation's Scientific Advisory Committee. Applicants will be notified of action taken on or before July 1, 1954.

SUBSTITUTION SEEN THREAT TO ALL LEVELS OF PHARMACY

The practice of drug "substitution," which is growing instead of waning, is a direct threat to all levels of the pharmaceutical industry while benefitting a short-sighted minority, according to Dr. Theodore G. Klumpp, president of Winthrop-Stearns, Inc.

Dr. Klumpp's remarks on "some of the drug industry's internal problems" were made in a talk at the mid-year luncheon meeting today (Jan. 26) of the Drug, Chemical and Allied Trades Section of the New York Board of Trade, at the Hotel Commodore. The title of his talk was "E Pluribus Unum."

The drug industry as a whole must recognize that it has a stake in curbing substitution, Dr. Klumpp declared. This practice is not only "an acute economic problem to the manufacturer, but an equally acute ethical and professional problem to the pharmacist.

"Other victims of substitution are the overwhelming majority of reputable pharmacists in the community who may be accused by the public of overcharging for prescriptions honestly compounded.

The laws of fair competition prized so highly by the drug industry are built around brand names, Dr. Klumpp said, adding that "the brand name gives fair trade its legal basis.

"To wipe out the brand name structure by substituting generic names is to wipe out the great protection against unfair competition which the retail druggist has worked so hard, for so long, to develop."

AMER. JOUR. DIG. DIS.

Dr. Klumpp cited "duplication" as a second serious industry problem. To meet this problem, he said, manufacturers have undertaken what no other industry known to me has done: to guarantee the sales of products by taking back for full credit any unsold items.

"In addition, we have undertaken the major effort and expense of moving our brands through detailing, advertising, sampling, direct mail and exhibits.

"At the same time, manufacturers are beginning to find out that duplicate products have a high mortality rate and don't often pay off."

Proposals to vest in the pharmacist the right to apply the generic name theory in compounding prescriptions "have not been fully thought through," Dr. Klumpp continued.

"To adopt such a proposal through legislative enactment would kill the fair trade laws, pave the way for grade labelling, which I consider foreign to a free enterprise economy, and would ultimately turn over more and more of the control and operation of the pharmaceutical industry to the government."

In referring to the National Pharmaceutical Council, recently organized, Dr. Klumpp stated that its purpose is to bring influence to bear against those practices of the few "that are undermining the ethical principles of fair competition and fair dealing upon which our industry must rest. The public responsibility and trust of this industry is too vital and precious to permit any erosion of our ethical standards and sound trade practices. We are not organized to drive a wedge between pharmacy and the manufacturers. It is our firm conviction that an industry divided against itself cannot stand."

NEW HOPE FOR SUFFERERS OF PARKINSON'S DISEASE; DOCTOR WRITES FIRST STUDY FOR LAYMAN

New York, N. Y.—Dr. John C. Button, Jr., nationally known neurologist and clinical investigator, has written the first study for the layman on Parkinson's Disease—the "shaking palsy"—which afflicts some half-million people in the United States alone.

His book, HOPE AND HELP IN PARKINSON'S DISEASE, (Vantage Press, $4.95), offers no "miracle cures." "But," Dr. Button declares, "there are simple, readily available drugs and treatments which, when properly combined, will usually bring about satisfactory improvement."

The book contains a list of all such drugs with dosages and methods of administration, which Dr. Button himself has used on hundreds of Parkinsonian victims at his Orange, New Jersey clinic.

The dread disease, the author explains, is a condition chiefly characterized by violent trembling and a progressive stiffening of all the muscles of the body, which attacks both sexes at any age. It sometimes follows old-fashioned flu, or may be caused by sleeping sickness or hardening of the arteries.

The ailment is named after Dr. James Parkinson, a London physician who lived in the early nineteenth century, and who himself suffered from shaking palsy. Dr. Parkinson's medical classic, *An Essay on the Shaking Palsy*, written in 1817, is reproduced in Dr. Button's book.

To Parkinson patients, Dr. Button says, "Do not sit around waiting for the millennium of miracles which will never arrive. Take advantage of what science can do now to relieve your distress."

Dr. Button's book is the result of 14 years of study and 50,000 miles of travel to clinics both in the United States and abroad. For the medical profession, it provides an authoritative and up-to-date reference work with a bibliography containing more than 700 titles.

YOUNG SCIENTISTS

Two and a half million teen-agers are reading about three girls named Mary who are young scientists at the Norwich Pharmacal Co. and its subsidiary, Eaton Laboratories, Inc., at Norwich, N. Y. An article entitled "Not All Science Is Fiction," in the February issue of Seventeen magazine, tells about the three Marys, their work, their plans for careers, and their common interests.

Every day the three Marys walk three blocks to work, meeting hundreds of other Norwich employes on the way. Then they don spotless white lab uniforms and each goes to her laboratory or shop to carry on scientific experiments or help develop engineering techniques. Each of the trio is 22 years old.

Mary Anne Robinson of Binghamton, N. Y., is a biochemist, helps with research projects and studies the effect of new drugs on laboratory animals. She hopes to continue her education, gain a Ph.D. degree, and do advanced university research work.

Mary Carol Armstrong of Johnson City, N. Y., is also a biochemist who expects to study medicine at the University of Geneva medical school in Switzerland. At present she is a control chemist, testing all of the drug ingredients that the Norwich Pharmacal Co. buys.

Mary Fleming of Syracuse, N. Y., works in the development engineering laboratory. She is a chemical engineer and a graduate of Syracuse University. Her job is to aid in formulating medicines and perfecting manufacturing techniques.

MEDICAL JOURNALISM SCHOLARSHIPS NEEDED

The obtaining of trained editorial assistants has always presented a problem to the staffs of medical periodicals and publishers, large clinics and hospitals, pharmaceutical and chemical companies, etc. The field is an interesting and lucrative one, but editors and publishers thus far have been unable to find applicants with any formal training in the field of medical writing and editing. Now, for the first time, courses in medical journalism are available at the schools of journalism of the Universities of Illinois and Missouri. These courses have been established through the efforts of the American Medical Writers' Association in conjunction with the interest and vision of the authorities of these schools. Members of the medical profession should know of these courses so that they may advise high school students and others who may be interested.

To help popularize these new collegiate medical journalism courses, the American Medical Writers' Association has established a Medical Journalism Scholarship Fund. The Association desires to make avail-

able continuing $500 scholarships at the University of Illinois, and at the University of Missouri. Physicians, medical publishers, pharmaceutical companies, and so forth, are cordially invited to join with members of the American Medical Writers' Association in building this Scholarship Fund. Dr. Harold Swanberg, Quincy, Ill., American Medical Writers' Association Secretary, has initiated the fund with a $1000 contribution for one $500 scholarship at each university (Ill. and Mo.) for 1954-1955, the first collegiate Medical Journalism Scholarships to be established.

The Association is incorporated not-for-profit, and contributions to it are exempt for income tax purposes. Checks should be made payable to the American Medical Writers' Ass'n., but all correspondence directed to Richard M. Hewitt, M.D., Chairman, Educational Committee A. M. W. A., Dept. of Publications, Mayo Clinic, Rochester, Minn.

geriatrone
elixir

delightfully flavored digestive-nutritive tonic

Each fluid ounce (approx. 2 tablespoonfuls) provides:
(alcohol 15% by volume)

digestive enzymes...	Digestive Enzymes:	
	pancreatin	126 mg.
	pepsin	126 mg.
	Betaine HCl	100 mg.
	Betaine Monohydrate	200 mg.
	Liver Concentrate*	220 mg.
lipotropics...	Yeast Extract*	220 mg.
	Vitamin B_{12}	4 mcg.
	Inositol	100 mg.
B complex vitamins...	Thiamine HCl (B_1)	4 mg.
	Riboflavin (B_2)	2 mg.
	Pyridoxine HCl (B_6)	2 mg.
	Panthenol	2 mg.
	Niacinamide	20 mg.
	Calcium Glycerophosphate	300 mg.
	Manganese Glycerophosphate	15 mg.

*provides whole natural vitamin B complex

Available in 16 oz. and gallon bottles.

For samples and detailed literature write

U S V

u. s. vitamin corporation
Casimir Funk Laboratories, Inc. (affiliate)
250 East 43rd Street, New York 17, N.Y.

POLIO

Due to delays in the manufacture of the trial polio vaccine the nationwide validity tests are expected to get under way in late March or early April, it was announced today by Basil O'Connor, president of the National Foundation for Infantile Paralysis.

Mr. O'Connor said it had been hoped that the injection of school children taking part in the tests could begin in February, but he added:

"We have been confronted with some of the usual production problems that have to be expected in the manufacutre of any new product. Added to these has been the length of time required to check and re-check the many processes involved in converting the results of any laboratory research into commercial production on a large scale. None of the problems encountered is insuperable and all are being rapidly solved."

Mr. O'Connor also said: "While production problems have postponed the date for the start of the trials, we plan to inoculate a sufficient number of children before June to determine scientifically the value of this product."

Preparation of large quantities of a trial vaccine involves a series of complicated steps, Mr. O'Connor explained.

"The virus is grown in tissue culture, a new technique," he stated. "Most of it is grown at the Connaught Medical Research Laboratories of the University of Toronto, where the tissue-culture process has been studied since 1949 under a grant from the National Foundation. More than sixty different ingredients are used to grow the virus in tissue culture, he said.

Polio virus grown in this way is shipped to pharmaceutical and biological concerns for conversion into vaccine, which requires several weeks.

Each lot of the vaccine is subjected to safety tests by three independent laboratories: the manufacturer's laboratory, the Virus Research Laboratory of the University of Pittsburgh and the Laboratory of Biologics Control of the National Institutes of Health in Washington.

The vaccine to be tested was de-

PARLUGUAN FOR PEPTIC ULCER MANAGEMENT and control of gastric hyperacidity

Now Troches Provide Effect of Intragastric Milk-Alkali Drip

Present day medical regimen is based on the generally accepted theory that to heal an uncomplicated gastroduodenal ulcer, hydrochloric acid should be neutralized. To reduce the acidity favors healing, as it most certainly favors relief of pain associated with ulcer symptoms.

The most effective method known for neutralizing stomach contents over long periods has been the continuous intragastric milk and alkali drip.

This method has practical disadvantages.

But now the principle and effect of the intragastric milk-alkali drip is provided by continuous sucking of PARLUGUAN buccal troches containing milk solids and non-systemic alkali.

PARLUGUAN buccal troches

- provide continuous acid neutralization
- promote healing of uncomplicated peptic ulcers
- reduce symptomatic ulcer pain
- strikingly reduce gastric acidity
- control pH levels for extended periods
- provide only 11 calories per troche
- are pleasant tasting

Also indicated for relief of gastric hyperacidity and gastritis.

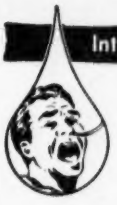
PARLUGUAN CONTAINS:

- Whole milk solids, fortified with dextrins and maltose
- Magnesium trisilicate
- Magnesium oxide
- Calcium carbonate
- Magnesium carbonate

DOSAGE: One-half hour after food is taken a PARLUGUAN troche should be placed in the mouth between the cheek and the gums and allowed to dissolve slowly over a period of 20 to 30 minutes. Up to 2 or 3 troches per hour may be required during the stage of ulcer activity. Follow-up treatment requires 1 to 2 troches between meals.

As an antacid for the temporary relief of gastric hyperacidity, 1 troche; repeat if necessary.

Trade Mark



Intubation . . . or . . . PARLUGUAN

Patient enjoys beneficial effect of intragastric milk-alkali drip without discomfort of intubation.

Available in handy vials of 25 troches at all pharmacies.
Samples and literature on request.

References:

Sandweiss, D. J.: W. P. Saunders, Phila., Peptic Ulcer, Chapter 28, 1951

Douthwaite, A. H.: Medical treatment of Peptic Ulcer, M. Press 227:195 (Feb. 27) 1952

Douthwaite, A. H. and Shaw, A. B.: The Control of Gastric Acidity, Brit. M. J. 2:180 (July 26) 1952

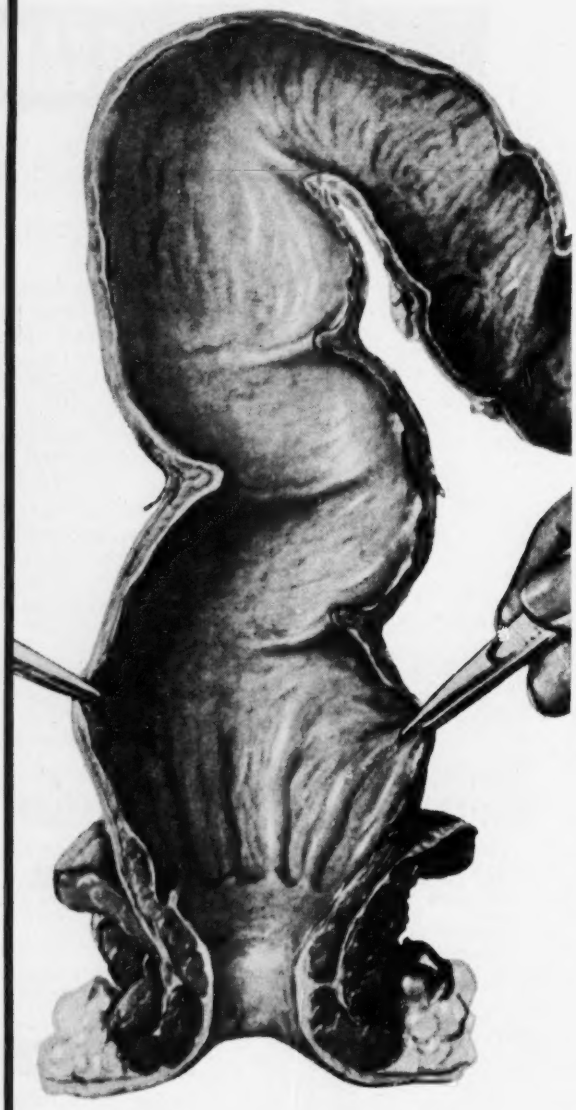
Panray CORP.

340 CANAL STREET, N. Y.

© 1953 The Panray Corp., New York

MUCOUS SURFACE OF THE PELVIC COLON, RECTUM, AND ANAL CANAL

The mucous membrane of the bowel performs an important absorptive function, but it is soft and readily subject to irritation. At times, the stools tend to become dry and hard, as when there has been delay in bowel evacuation. The resultant inspissated stool masses may lead to irritation of the bowel mucosa.



HABIT TIME OF BOWEL MOVEMENT

In constipation, the restoration of regularity is facilitated by PETROGALAR. By providing bland, unabsorbable fluid, PETROGALAR helps keep the feces soft, moist, and easy to evacuate. It affords an efficient treatment to help the patient reestablish and maintain *Habit Time of Bowel Movement.*

PETROGALAR®

Aqueous suspension of mineral oil, plain

Supplied: Bottles of 1 pint

Wyeth®

Philadelphia 2, Pa.

veloped under a March of Dimes grant by Dr. Jonas E. Salk of the University of Pittsburgh and is currently being produced on a non-profit basis by Cutter Laboratories, Berkeley, Calif.; Eli Lilly and Co., Indianapolis; Parke Davis & Co., Detroit; Pitman-Moore Co., Indianapolis, and Wyeth Laboratories, Philadelphia.

Dr. Salk announced recently that he was extending his studies to at least 5,000 persons in Allegheny County, Penna., before the start of the National Foundation field trials. He was unable to resume this work earlier because polio cases continued to occur through December in that area.

A small amount of the commercially-produced vaccine will be available for Dr. Salk's studies in February, it is believed, but the large quantities needed for the field trials cannot be processed, tested and packaged for shipment before the last week in March, Mr. O'Connor said.

The vaccine trials are being organized with the advice of the National Foundation's scientific committees and that of special committees appointed by the Association of State and Territorial Health Officers, with Dr. Hart E. Van Riper, National Foundation medical director, in charge of the project. The test areas are being selected upon recommendation of individual State Health Officers, based on scientific criteria.

Lists of all eligible counties are being compiled and studied, Mr. O'Connor said, but the final number chosen must depend upon the supply of trial vaccine available.

Mr. O'Connor said the National Foundation has received excellent cooperation from all state health officials in planning the tests.

"However," he said, "no final determination of locations of trial areas can be made at this time and no definite commitment will be asked of any health officer until Dr. Salk completes his additional 5,000 inoculations in Allegheny County."

TREVIDAL—BALANCED ANTACID—RELEASED BY ORGANON

Trevidal, the much-heralded, balanced antacid tablet, has just been

'TRICOLOID' brand
TRICYCLAMOL

New...
for peptic ulcer
or gastrointestinal
spasm

'TRICOLOID' brand
TRICYCLAMOL

released by Organon Inc. of Orange, N. J. Trevidal offers in each tablet four commonly employed antacid ingredients, balanced to relieve gastric hyperacidity without causing constipation or diarrhea and without causing alkalinosis; a vegetable mucin for protective coating of the wall of the stomach and duodenum; and a protein binder for gradual release of the antacid ingredients.

Trevidal tablets need not be chewed, merely swallowed with a small amount of water, for they disintegrate rapidly in the stomach. Magnesium trisilicate, aluminum hydroxide gel, calcium carbonate, and magnesium carbonate are the four antacids providing effective relief in the treatment of peptic ulcer and in relieving symptoms of gastric hyperacidity. Regonol (T.M.), a vegetable mucin, provides a protective coating for not only the wall of the stomach and duodenum, but also the ulcer itself to allow healing to occur more rapidly. Egraine (T.M.), a protein binder from oat, acts to release each of the acid buffering ingredients slowly, providing maximum effectiveness.

As an antacid, the dosage of Trevidal is one or two tablets with water whenever symptoms of gastric distress occur. Relief from gastric distress can be expected for approximately 2 hours after ingestion of the tablets. Dose may be repeated 4 to 5 times daily, between meals, and at bedtime, or according to the physician's orders. Trevidal follows Organon's ethical line of products and is not advertised to the laity. Descriptive literature is available on request.

for the "squeeze" of g.i. spasm
antispasmodic action
virtually without atropinism . . .
through the selective spasmolysis
of homatropine methylbromide
(one-thirtieth as toxic as atropine)
plus the sedation of phenobarbital
Each yellow tablet of MESOPIN-PB
or teaspoonful of yellow elixir
contains 2.5 mg. homatropine methylbromide and 15 mg. phenobarbital.
Also available as
MESOPIN Plain (without phenobarbital)
in white tablets, green elixir, and powder.
MESOPIN-PB
(Homatropine Methylbromide and Phenobarbital)
Endo
Samples? Just write to:
Endo Products Inc., Richmond Hill 18, New York

INDEX TO ADVERTISERS

American Meat Institute III
Ames Company, Inc. VI
Burroughs Wellcome & Co. II
Burroughs Wellcome & Co. XV
Ciba VIII
Endo Products, Inc. XVI
Massengill Co. V
Organon, Inc. IV
Panray Corporation XIII
Chas. Pfizer & Co. ..... 3rd Cover
G. D. Searle & Co. ..... 4th Cover
Schering Corp. VII
U. S. Vitamin Corporation XII
Winthrop-Stearns, Inc. I
Wyeth, Inc. ..... 2nd Cover
Wyeth, Inc. XIV

preferred
antibiotic therapy
for gastrointestinal
infections . . .

Terramycin®

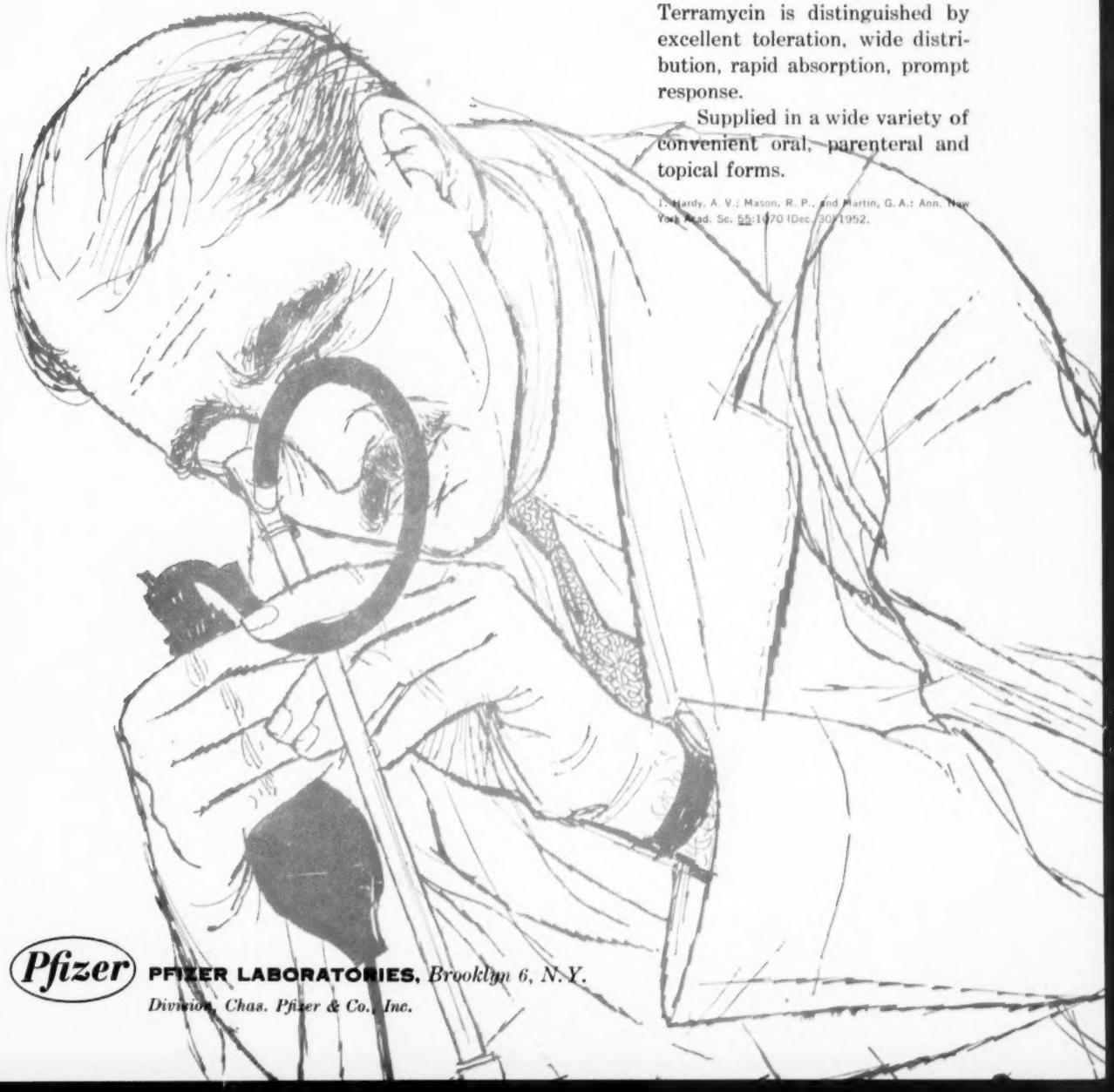
brand of oxytetracycline

Regarded as "the antibiotic of first choice"[1] in the treatment of bacillary dysentery, Terramycin has been widely used by gastroenterologists and their colleagues in the successful treatment of amebiasis, salmonella and shigella infections, in infectious diarrhea, and other gastrointestinal infections due to sensitive organisms within its broad spectrum of antimicrobial activity.

Clinically, treatment with Terramycin is distinguished by excellent toleration, wide distribution, rapid absorption, prompt response.

Supplied in a wide variety of convenient oral, parenteral and topical forms.

1. Hardy, A. V.; Mason, R. P., and Martin, G. A.: Ann. New York Acad. Sc. 55:1070 (Dec. 30) 1952.



Pfizer **PFIZER LABORATORIES,** *Brooklyn 6, N.Y.*
Division, Chas. Pfizer & Co., Inc.

Fig. 1 "Roentgen examination . . . revealed the ulcer to be very much in evidence."

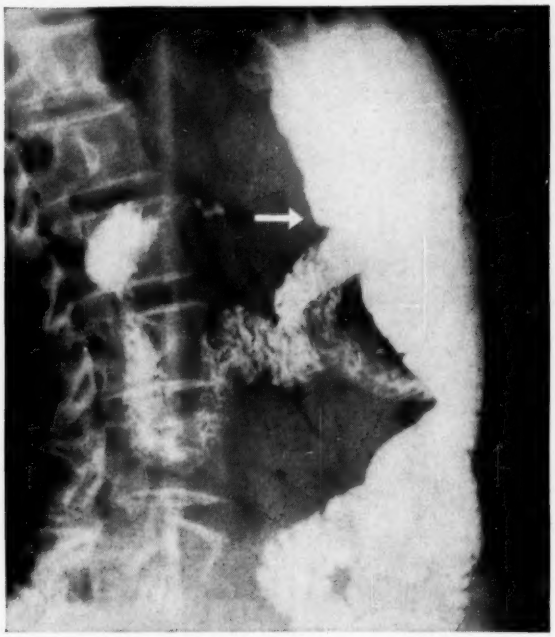


Fig. 2 In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

Clinical Evaluation of Pro-Banthine®

The case report described below offers significant evidence of the high potency in low dosage of the new, well-tolerated anticholinergic agent, Pro-Banthine.

"M. D., female, aged 48, had a posterior gastrojejunostomy 14 years ago for duodenal ulcer. The patient was fairly well until nine months ago when severe, intractable pains occurred. She was hospitalized and a subtotal gastrectomy was done.

"She remained well for only a few months and was referred to us because of recurrence of very severe pain and marked weight loss. Roentgen study revealed a fairly large ulcer niche on the gastric side of the anastomosis.

"The patient had been on various types of antacids and sedatives without relief from pain. She was given 60 mg. of Pro-Banthine q.i.d. and within 72 hours was able to sleep through the night for the first time in weeks.

"At the end of two weeks of such treatment the patient had absolutely no pain and felt that she had been 'cured.' Roentgen examination at this time revealed the ulcer to be very much in evidence (*Fig. 1*). Much persuasion was necessary to make the patient realize the importance of maintaining her diet and therapy.

"Ten weeks of controlled regulation was necessary before we were satisfied that the ulcer niche was no longer in evidence roentgenologically or gastroscopically (*Fig. 2*).

"She has been maintained on 30 mg. [q. i. d.] of Pro-Banthine for almost five months with no recurrence of symptoms."[1]

Pro-Banthine (*brand of propantheline bromide*), the new, improved anticholinergic agent, is more potent and, consequently, a smaller dosage is required and side effects are greatly reduced or absent. It is available in 15 mg. tablets as well as in tablets (15 mg.) with Phenobarbital (15 mg.) and in 30 mg. ampuls.

Peptic ulcer, gastritis, intestinal hypermotility, pancreatitis, genitourinary spasm and hyperhidrosis respond effectively to Pro-Banthine, orally, combined with dietary regulation and mental relaxation. G. D. Searle & Co. *Research in the Service of Medicine.*

---

1. Schwartz, I. R.: Personal communication, Feb. 9, 1953.